THE SULFONAMIDES

SHARP & DOHME

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Foreword

Bacterial chemotherapy received a tremendous impetus in 1937 with the introduction of sulfanilamide. The success of this original sulfonamide in combating certain infections initiated a display of intense activity in research laboratories all over the world . . . activity that, in the succeeding ten years, gave birth to other sulfonamides—more effective and better tolerated!

Now that the original enthusiasm and optimism have been tempered by time, and claims and counter-claims have been examined and evaluated, leadership in sulfonamide research becomes evident.

Today the Medical Research Laboratories of Sharp & Dohme, by virtue of early and persistent work, have assumed a dominant position in sulfonamide development. Sharp & Dohme is credited officially with the development of five of the seven most effective compounds and sharing in the development of a sixth.

Specifically, Sharp & Dohme was the first to synthesize any pyrimidine derivative of sulfanilamide and holds basic patents dominating all three drugs in this group—namely, sulfamerazine, sulfadiazine and sulfamethazine. Sharp & Dohme synthesized the intestinal sulfonamides, 'Sulfasuxidine' succinylsulfathiazole and 'Sulfathalidine' phthalylsulfathiazole. Sharp & Dohme shared in the development of sulfathiazole.

Credit for this enviable record in development of antibacterial drugs belongs, of course, to Sharp & Dohme's Medical Research Staff —those men and women whose devotion to and zeal for development of outstanding therapeutic agents for the medical profession is as brilliant in other fields as it is in the sulfonamides.

Since the sulfonamides occupy such an important place in today's therapeutic armamentarium, the physician will find this booklet of particular value for quick, concise sulfonamide information. Presented here are the formulas, characteristics, indications and dosage of six frequently prescribed sulfonamides. The physician also will find information on how these compounds are supplied, plus brief abstracts of recent articles on their therapeutic use.

SHARP & DOHME

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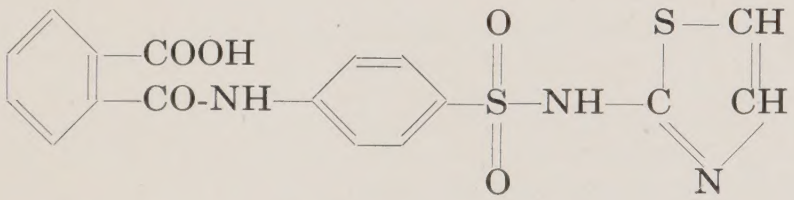
'Sulfathalidine'

PHTHALYLSULFATHIAZOLE

Formula: 'Sulfathalidine' phthalylsulfathiazole is a dicarboxylic acid derivative of sulfathiazole synthesized in the Medical Research Laboratories of Sharp & Dohme. Phthalylsulfathiazole is the short, common name for the chemical compound, 2-(N^4-phthalylsulfanilamido)-thiazole, represented by the structural formula



It is a white, crystalline powder practically insoluble in water and weak acid. It is dissolved by an excess of an aqueous solution of sodium bicarbonate or sodium carbonate at room temperature with the liberation of carbon dioxide.

Characteristics: 'Sulfathalidine' phthalylsulfathiazole is an enteric sulfonamide. It is administered orally in low dosage and is characterized by little or no toxicity.

The compound maintains a high concentration in the gastrointestinal tract where its bacteriostatic action markedly alters the bacterial flora and results in a profound reduction of Escherichia coli, clostridia and related organisms. Feces become soft and odorless. The compound is an effective bacteriostat in the presence of a watery diarrhea.

An average of only 5 per cent of the ingested drug is absorbed from the bowel, and this is excreted rapidly by the kidneys. Crystalluria has not been observed.

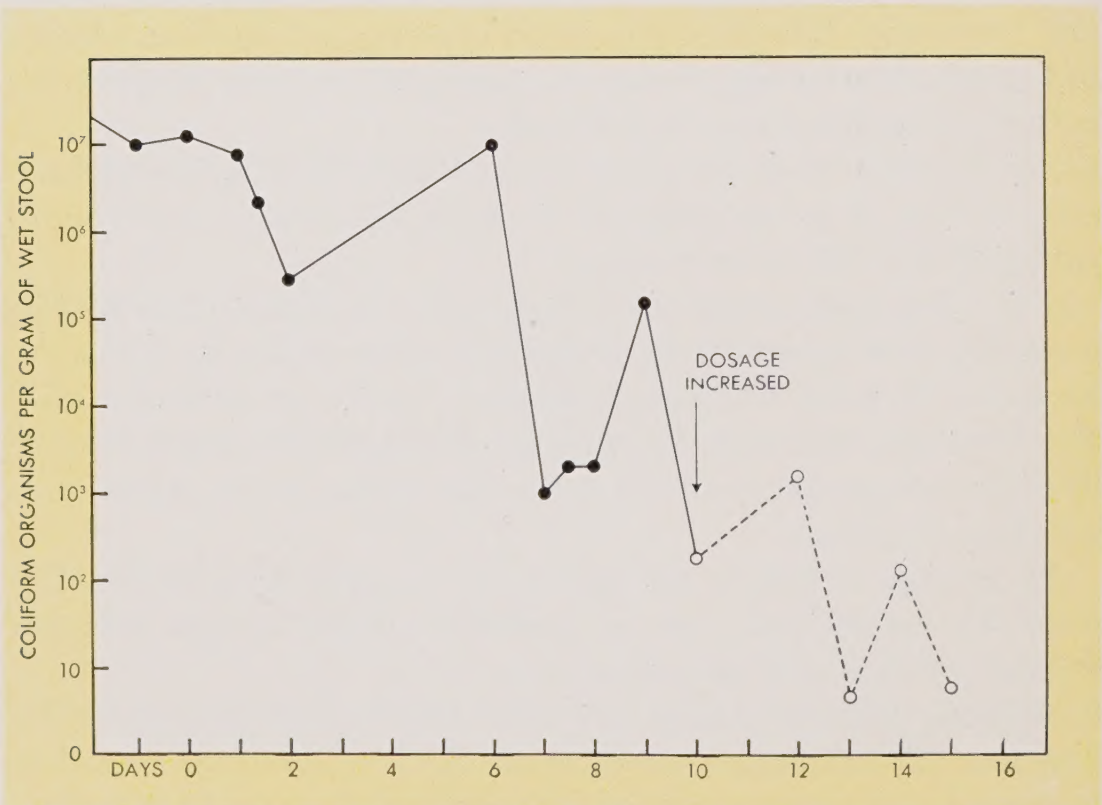
Indications: Clinical studies and actual use have established 'Sulfathalidine' phthalylsulfathiazole as an effective therapeutic agent in treatment and management of inflammatory diseases of the colon.

The drug has proved particularly effective in treatment of patients with *ulcerative colitis*. Its administration has resulted in a favorable response in both the *acute* and *chronic* forms of the disease. The bacteriostatic action minimizes the extent of the ulcerative lesions by reducing the number of secondary invaders. The drug has been administered continuously for more than ten months without causing toxic reactions.

'Sulfathalidine' phthalylsulfathiazole has demonstrated its value in treatment of *regional ileitis* and *ileojejunitis*. It is effective not only for preoperative use but also for treatment of recurrences following surgery.

The efficiency of phthalylsulfathiazole when administered in the presence of a watery diarrhea as reflected by alteration of the coliform count in the gastrointestinal tract of man. Watery diarrhea was maintained by administration of one ounce of magnesium sulfate every 12 hours for 15 days. Phthalylsulfathiazole was administered at first in 6 divided doses at 4 hour intervals on the basis of 0.125 Gm./Kg. of body weight. On the tenth day the dose was increased to 0.25 Gm./Kg. daily.*

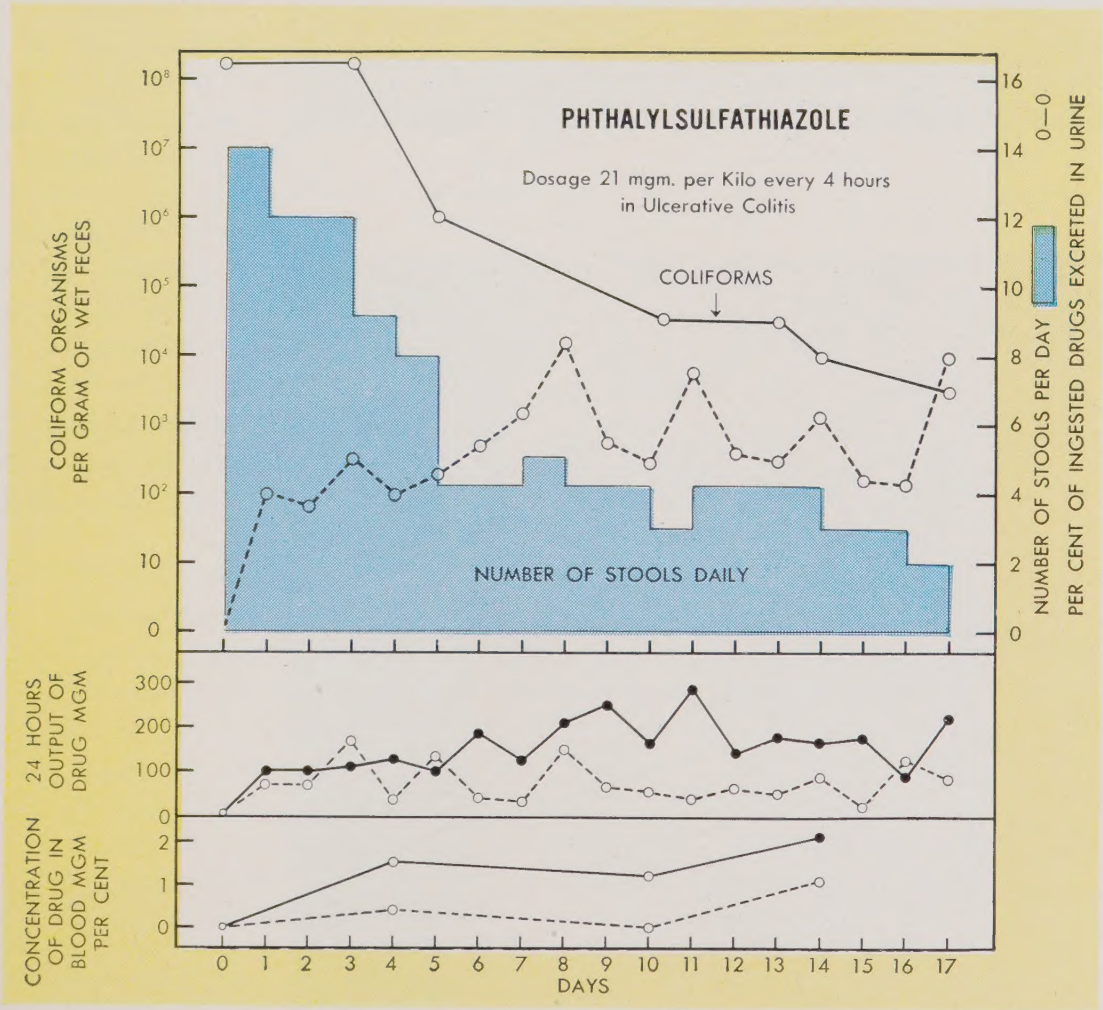
**From Poth, E. J., and Ross, C. A., J. Lab. & Clin. Med. 29:785, Aug. 1944.*

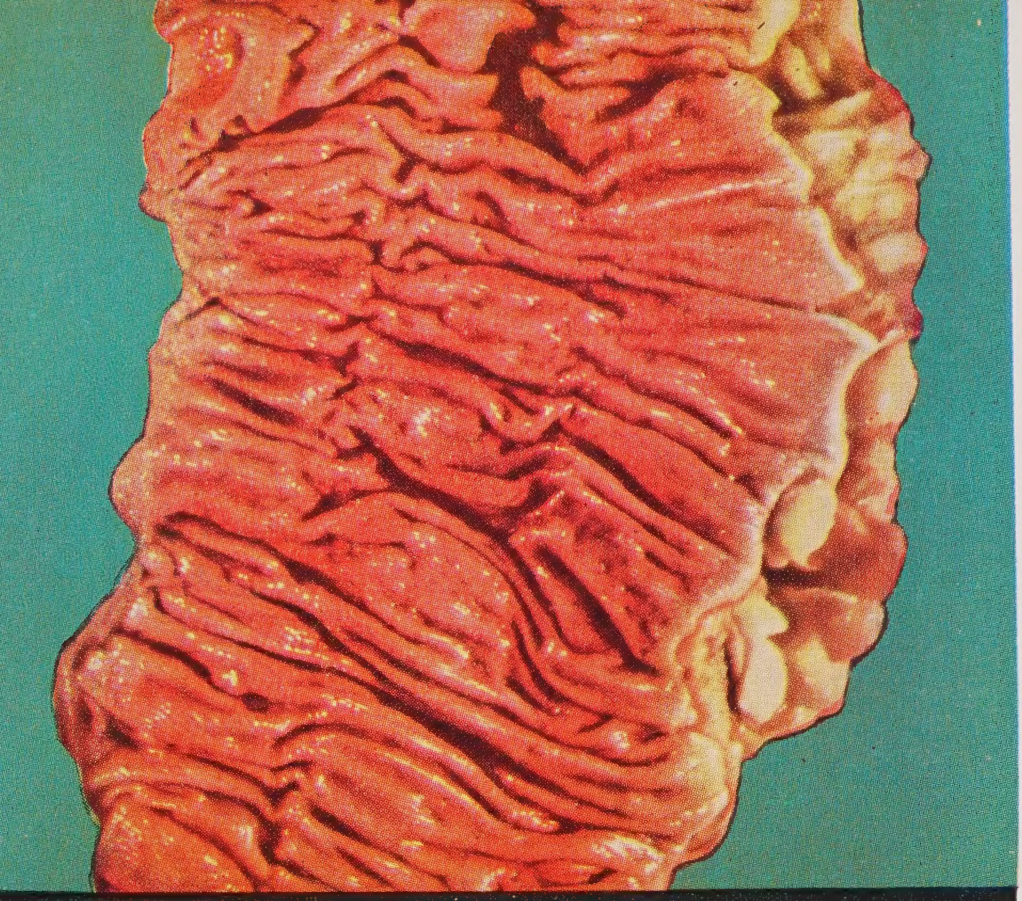


'Sulfathalidine' phthalylsulfathiazole is indicated also in *preoperative preparation* and *postoperative treatment* of patients undergoing *intestinal surgery*. Because of its effect upon the bacterial flora, it reduces the incidence of peritonitis and abscess formation, and results in a smoother and easier postoperative course for the patient.

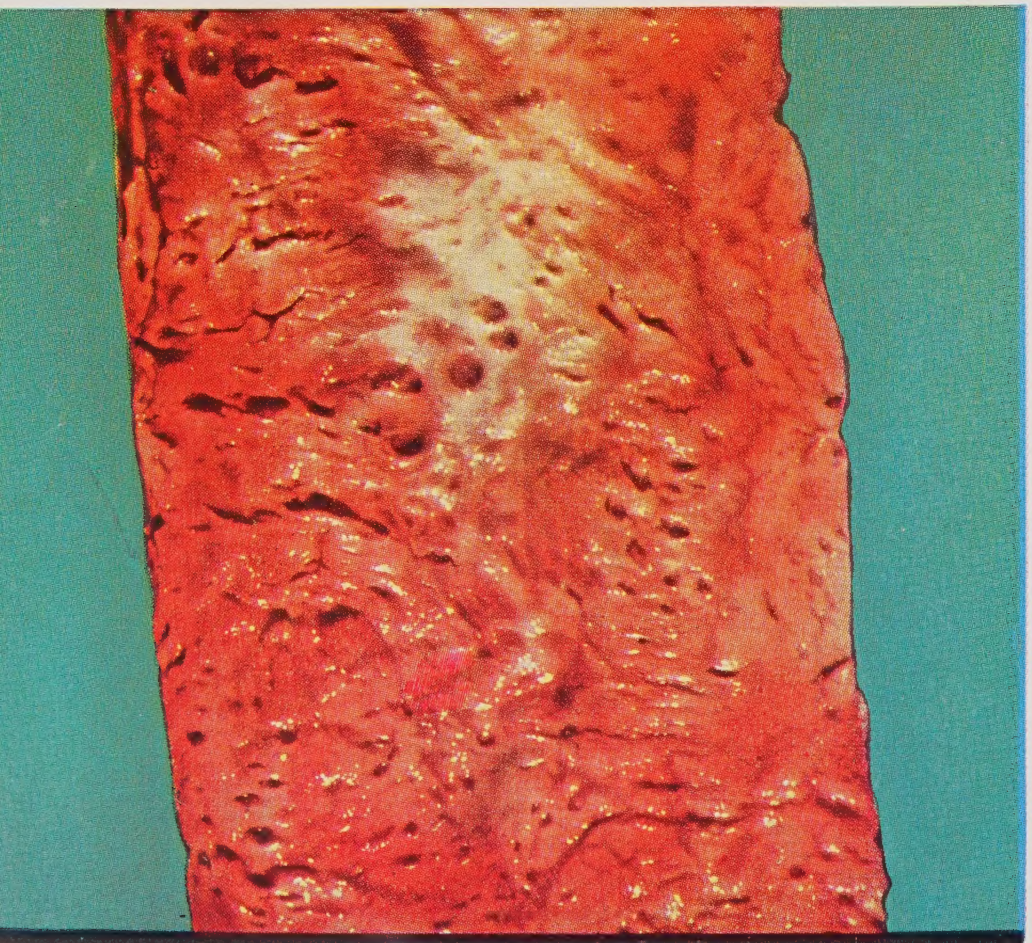
Effect of phthalylsulfathiazole in ulcerative colitis. Illness of 5 years' duration with a daily average of 14 stools containing blood and mucus. Number of stools decreased to 4 after 5 days' administration of phthalylsulfathiazole. Blood and mucus disappeared and stools were formed, odorless and of normal appearance. On a liberal bland diet and continuation of phthalylsulfathiazole over a period of 12 weeks, no evidence of toxicity was observed. Stools decreased to 2 daily and patient improved generally and gained steadily in weight.*

**From Poth, E. J., and Ross, C. A., J. Lab. & Clin. Med. 29:785, Aug. 1944.*


PHTHALYLSULFATHIAZOLE
Dosage 21 mgm. per Kilo every 4 hours in Ulcerative Colitis
COLIFORMS
NUMBER OF STOOLS DAILY
COLIFORM ORGANISMS PER GRAM OF WET FECES
NUMBER OF STOOLS PER DAY 0—0
PER CENT OF INGESTED DRUGS EXCRETED IN URINE
24 HOURS OUTPUT OF DRUG MGM
CONCENTRATION OF DRUG IN BLOOD MGM PER CENT
DAYS



THE NORMAL BOWEL



ULCERATIVE COLITIS

Ulcerative colitis, one of the most insidious of intestinal infections, yields to administration of 'Sulfathalidine' phthalylsulfathiazole. This nontoxic sulfonamide is effective in treatment of both the acute and chronic forms of the disease. After therapy with the drug, stools become formed and odorless, blood in stools disappears, cramping in abdomen usually subsides within 48 hours, and evacuations are reduced substantially.

Dosage: Administered in daily doses of 0.05 Gm. to 0.1 Gm. per kilogram of body weight. The total daily dose should be administered in equally divided doses at four to six hour intervals. See page 46 for detailed dosage schedule.

How Supplied: 'Sulfathalidine' phthalylsulfathiazole is supplied in 0.5-Gm. compressed tablets in bottles of 100, 500 and 1,000.

Abstracts

Ulcerative Colitis

Poth, E. J.: Sulfasuxidine* and Sulfathalidine,* Texas Rep. Biol. & Med. *4*:68-102, Spring 1946.

Although an absolute cure is not obtained, the use of 'Sulfathalidine' phthalylsulfathiazole and 'Sulfasuxidine' succinylsulfathiazole in chronic ulcerative colitis frequently induces and maintains a remission of the disease, and on occasion the effect is dramatic. Either drug must be administered in full therapeutic dosage for months. Phthalylsulfathiazole apparently is better tolerated and is the drug of choice. In some instances anal fistulas have healed. Although irreversible anatomic changes may ultimately require colectomy, the patient shows marked improvement and is better prepared for operation.

Streicher, M. H.: Phthalylsulfathiazole ('Sulfathalidine'*). Clinical, Chemical and Bacteriologic Evaluations in Infectious Diseases of the Colon, J. A. M. A. *129*:1080-1083, Dec. 15, 1945.

Phthalylsulfathiazole was effective in the treatment of 90 out of 100 patients with ulcerative lesions and other inflammatory conditions of the colon. Improvement was noted in patients with acute as well as chronic ulcerative colitis. Cramping in the abdomen subsided, evacuations were reduced in number, the stools became odorless, and blood in the stools disappeared. Some patients received the drug for nine months without toxic reactions. The author concludes that "phthalylsulfathiazole is less toxic and more bacteriostatic than any intestinal agent used previously and that . . . smaller doses of this drug may be used to advantage."

* 'Sulfasuxidine' and 'Sulfathalidine' are Sharp & Dohme trade-marks respectively for succinylsulfathiazole and phthalylsulfathiazole.

Streicher, M. H.: Sulfathalidine*: Clinical Evaluation in Infectious Diseases of the Colon, Illinois M. J. *88*:85-87, Aug. 1945.

'Sulfathalidine' phthalylsulfathiazole possesses strong bacteriostatic properties when administered in doses of 0.125 Gm. per kilogram of body weight every four hours. The drug was effective in both acute and chronic cases of ulcerative colitis. Improvement was observed in all of the acute cases and in 30 of 35 chronic cases.

Cramping in the abdomen subsided within forty-eight hours, blood in the stools disappeared, the stools became formed and odorless, and the number of evacuations were reduced. Fever in the acute cases was reduced within from forty-eight to seventy-two hours following administration of phthalylsulfathiazole.

Bargen, J. A.: Sulfathalidine* in Intestinal Disease, Proc. Staff Meet., Mayo Clin. *20*:85-87, March 21, 1945.

In the treatment of acute and chronic streptococcic ulcerative colitis with phthalylsulfathiazole, a favorable response was observed in 26 patients, fair in 1, slight in 1, and no response in 9. Response was judged by reduction in bowel motion, decrease or disappearance of blood from the stools, and relief from symptoms of toxemia. 'Sulfathalidine' phthalylsulfathiazole has certain advantages over other drugs employed for the treatment of intestinal conditions, since it is less toxic, is effective in smaller dosage, and produces favorable results when other drugs are ineffective or cause toxic reactions.

Poth, E. J., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, J. Lab. & Clin. Med. *29*:785-808, Aug. 1944.

Six patients with chronic ulcerative colitis responded satisfactorily to treatment with 'Sulfathalidine' phthalylsulfathiazole in a dosage of 0.02 Gm. per kilogram of body weight every four hours. One patient received the drug continuously for ten months without evidence of toxic reactions.

"The number of cases treated is too small to draw any definite conclusions, but it appears that this compound is at least as effective as any of the other sulfonamides in bringing about and maintaining the patient in a remission."

* See footnote page 7.

Regional Ileitis

Poth, E. J.: Sulfasuxidine* and Sulfathalidine*, Texas Rep. Biol. & Med. *4*:68-102, Spring 1946.

In the treatment of regional ileitis or Crohn's disease, 'Sulfathalidine' phthalylsulfathiazole and its companion sulfonamide, 'Sulfasuxidine' succinylsulfathiazole, are effective not only for preoperative use but also for treatment of recurrences after resection or short-circuiting operations. The value of these two drugs in the initial treatment of the disease is emphasized, and there is evidence also that surgical treatment should be obviated frequently by the prolonged use of these sulfonamides.

Bargen, J. A.: Sulfathalidine* in Intestinal Disease, Proc. Staff Meet., Mayo Clin. *20*:85-87, March 21, 1945.

Clinical improvement following 'Sulfathalidine' phthalylsulfathiazole therapy was observed in the treatment of three patients with regional ileitis and one patient with regional ulcerative colitis. Marked improvement in intestinal symptoms was noted in two of the three patients with regional ileitis and slight improvement in the third.

Garlock, J. H., and Crohn, B. B.: An Appraisal of the Results of Surgery in Treatment of Regional Ileitis, J. A. M. A. *127*:205-208, Jan. 27, 1945.

The authors report that patients with recurrences of regional ileitis following surgery often improve after therapy with 'Sulfathalidine' phthalylsulfathiazole or 'Sulfasuxidine' succinylsulfathiazole. Supportive measures such as diet, liver extract and vitamin B injections are helpful.

Surgery

Bargen, J. A.: The Use of the Newer Sulfonamides and Antibiotics in Intestinal Diseases, M. Clin. North America *30*:919-931, July 1946.

With the use of 'Sulfathalidine' phthalylsulfathiazole and 'Sulfasuxidine' succinylsulfathiazole in the treatment of the active stage of diverticulitis, it frequently is unnecessary to resort to surgery. When surgery is required, the acute infectious and perforative

* See footnote page 7.

stage may be minimized by the use of either drug to the extent that operative intervention is less hazardous. The preoperative use of phthalylsulfathiazole or succinylsulfathiazole is an important factor in making operations on the intestine safer, particularly in cases of neoplastic intestinal lesions. Intestinal instillation is the route employed in cases of fistula, or where ileostomy or subsequent closure or resection of the large intestine is required.

Thomson, R., and Daland, E. M.: The Use of Phthalylsulfathiazole (Sulfathalidine*) in Colonic Surgery, New England J. Med. *234*:431-433, March 28, 1946.

Phthalylsulfathiazole was an effective intestinal bacteriostatic agent in the preoperative preparation of 51 patients undergoing surgery of the large bowel. Administration of the drug was begun five or six days before operation in an initial dosage of 0.05 Gm. per kilogram of body weight followed by 1 Gm. every four hours day and night. At operation the bowel was found to be clean, and there was no evidence of distention. The mortality rate was 2 per cent and the incidence of wound infection 8 per cent. More extensive postoperative use might reduce the risk from soiling of the peritoneal cavity.

Angelo, G.: Phthalylsulfathiazole—'Sulfathalidine': A Clinical Evaluation in 122 Patients with Proctologic and Related Conditions, Am. J. Surg. *70*:354-359, Dec. 1945.

Phthalylsulfathiazole was administered during the twenty-four to forty-eight hour period before operation in anorectal surgery, and for three to five days prior to operation in large bowel surgery. Postoperative administration was continued for ten days to three weeks. End to end anastomosis was possible without high incidence of serious complications. The necessity for purgatives and enemas was reduced; the bowel became clean and the stools soft and gelatinous. Distention and postoperative discomfort were minimized and spontaneous evacuation occurred early. Phthalylsulfathiazole caused a considerable reduction in the number of coliform organisms and was responsible for a marked decrease in the incidence of peritonitis.

Poth, E. J.: Succinylsulfathiazole and Phthalylsulfathiazole in Surgery of the Colon, Surgery *17*:773-780, June 1945.

The mortality rate following surgery of the colon is lowered considerably by the preoperative use of phthalylsulfathiazole or suc-

* See footnote page 7.

cinylsulfathiazole. Usually 1.5 Gm. of phthalylsulfathiazole is administered every four hours for seven days, and twice this amount if a watery diarrhea is present. If a cleansing enema is desirable it should consist of sterile, warm, tap water containing 6 Gm. of phthalylsulfathiazole per liter. In the presence of an obstruction, the drug should be administered orally, and it also should be introduced into the distal segment of the bowel to reduce the number of organisms in this portion. Phthalylsulfathiazole, 1.5 Gm. every four hours, is the drug of choice for postoperative treatment.

Bacon, H. E., Todhunter, W. D., Gass, O. C., and Wolfe, F. D.: The Preoperative and Postoperative Treatment of Cancer of the Rectum and Pelvic Colon, J. Internat. Coll. Surgeons *8*:20-32, Jan.-Feb. 1945.

'Sulfathalidine' phthalylsulfathiazole was administered preoperatively and postoperatively in a dosage of 0.1 Gm. per kilogram of body weight every four hours to 54 patients undergoing resections of the colon, including 19 proctosigmoidectomies. Administration of the drug was begun at least four days before operation and was resumed as soon as the patient could tolerate liquid by mouth. This drug proved to be effective in reducing the number of coliform organisms. In 11 cases gross contamination of the peritoneal cavity with fecal material occurred without fatality. In no instance were untoward reactions encountered.

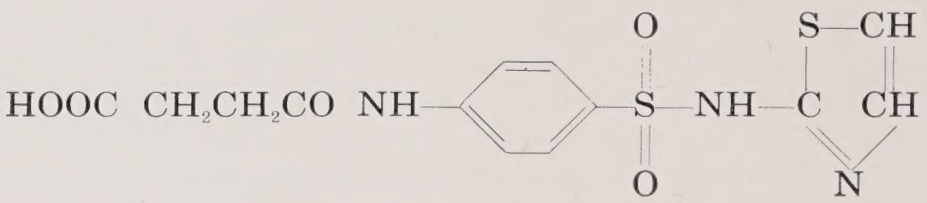
Poth, E. J., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, J. Lab. & Clin. Med. *29*:785-808, Aug. 1944.

'Sulfathalidine' phthalylsulfathiazole is an effective antibacterial agent in the preoperative and postoperative treatment of patients undergoing surgery of the colon. The bacteriostatic effect of phthalylsulfathiazole on coliform organisms, in one-half the dosage, is as great as that of succinylsulfathiazole. Since the drug is effective even in the presence of a watery diarrhea, it permits preoperative purgation when it is desired to clear the bowel. It is valuable also when diarrhea is present such as is encountered frequently with malignancies of the cecum and ascending colon.

'Sulfasuxidine'

SUCCINYLSULFATHIAZOLE

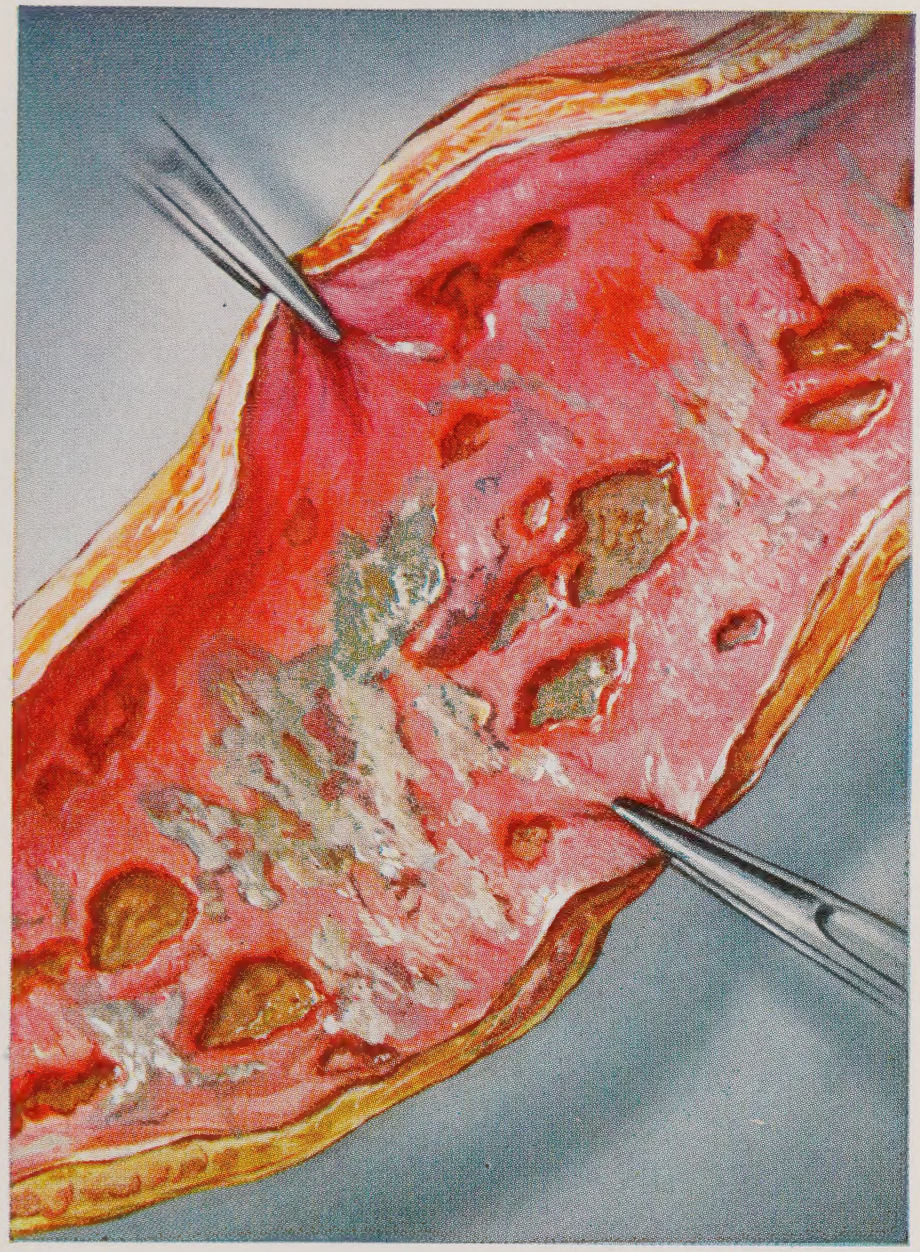
Formula: 'Sulfasuxidine' succinylsulfathiazole is a dicarboxylic acid derivative of sulfathiazole synthesized in the Medical Research Laboratories of Sharp & Dohme. Succinylsulfathiazole is the short common name for the chemical compound 2-(p-succinyl aminobenzenesulfonamido)-thiazole, represented by the structural formula



It is a white, crystalline powder sparingly soluble in alcohol, acetone and water, but readily soluble in sodium bicarbonate solution.

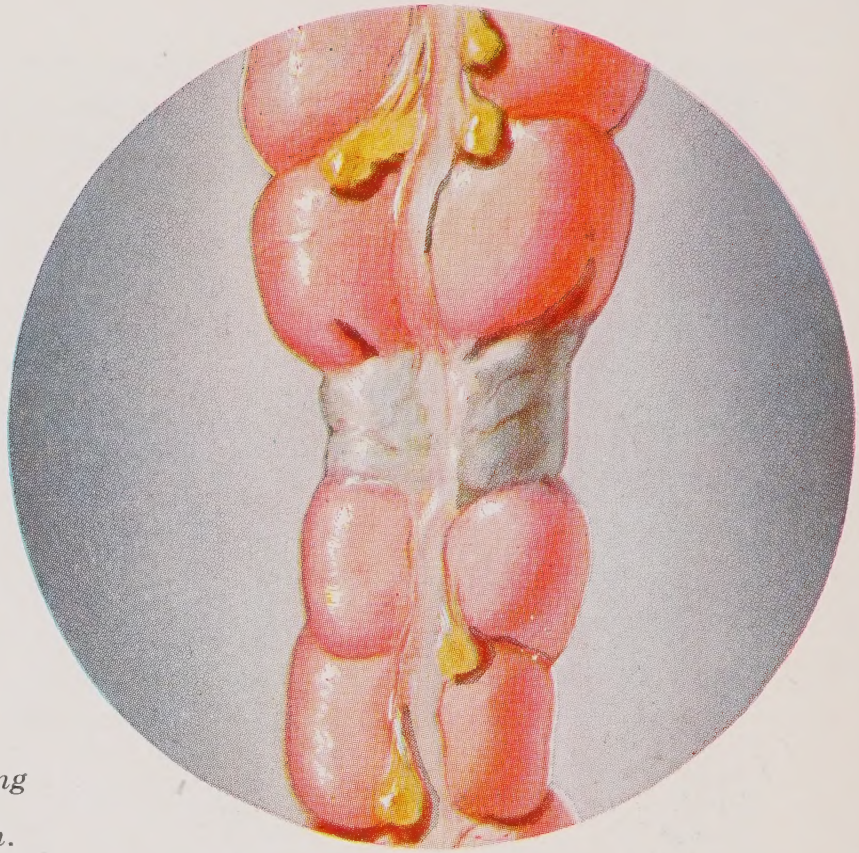
Characteristics: 'Sulfasuxidine' succinylsulfathiazole is an enteric sulfonamide that is relatively nontoxic in therapeutic doses. It maintains a high concentration in the gastrointestinal tract and a low concentration in the blood. It is poorly absorbed from the bowel, and an average of only 5 per cent of the ingested drug is excreted by the kidneys.

The bacteriostatic action of the compound markedly alters the bacterial flora and rapidly reduces the number of Escherichia coli and related organisms. Feces become semifluid and practically odorless. Dysentery bacilli such as Shiga, Flexner and Sonne strains are susceptible to the bacteriostatic action of 'Sulfasuxidine' succinylsulfathiazole. The drug is also effective in the presence of ulcerating lesions in the bowel.

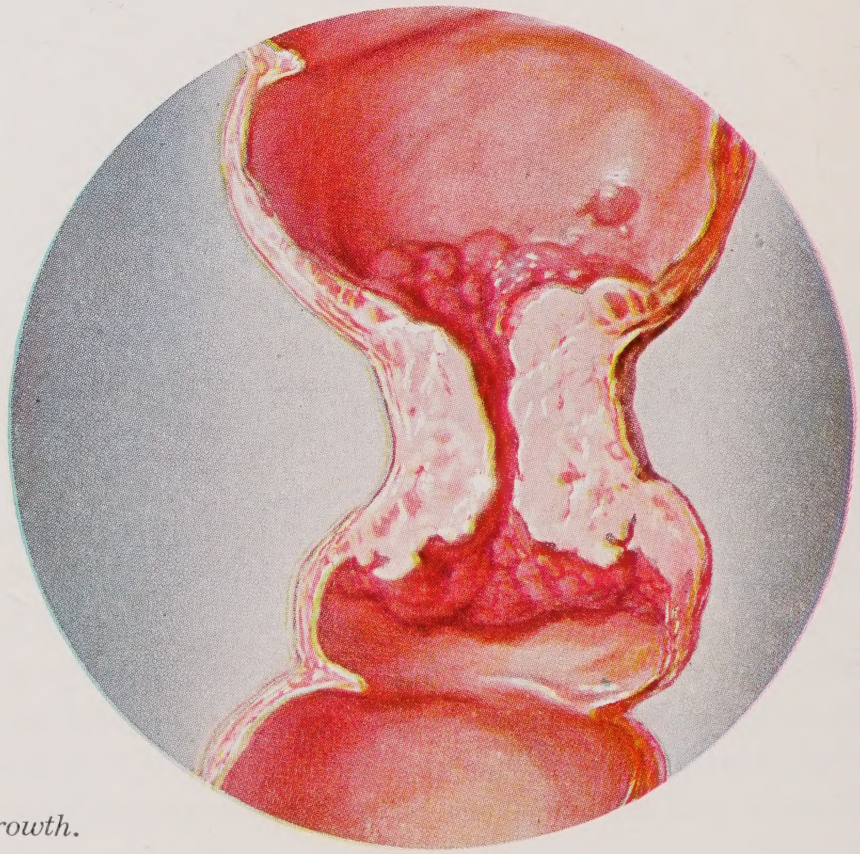


Appearance of intestinal mucosa in bacillary dysentery.

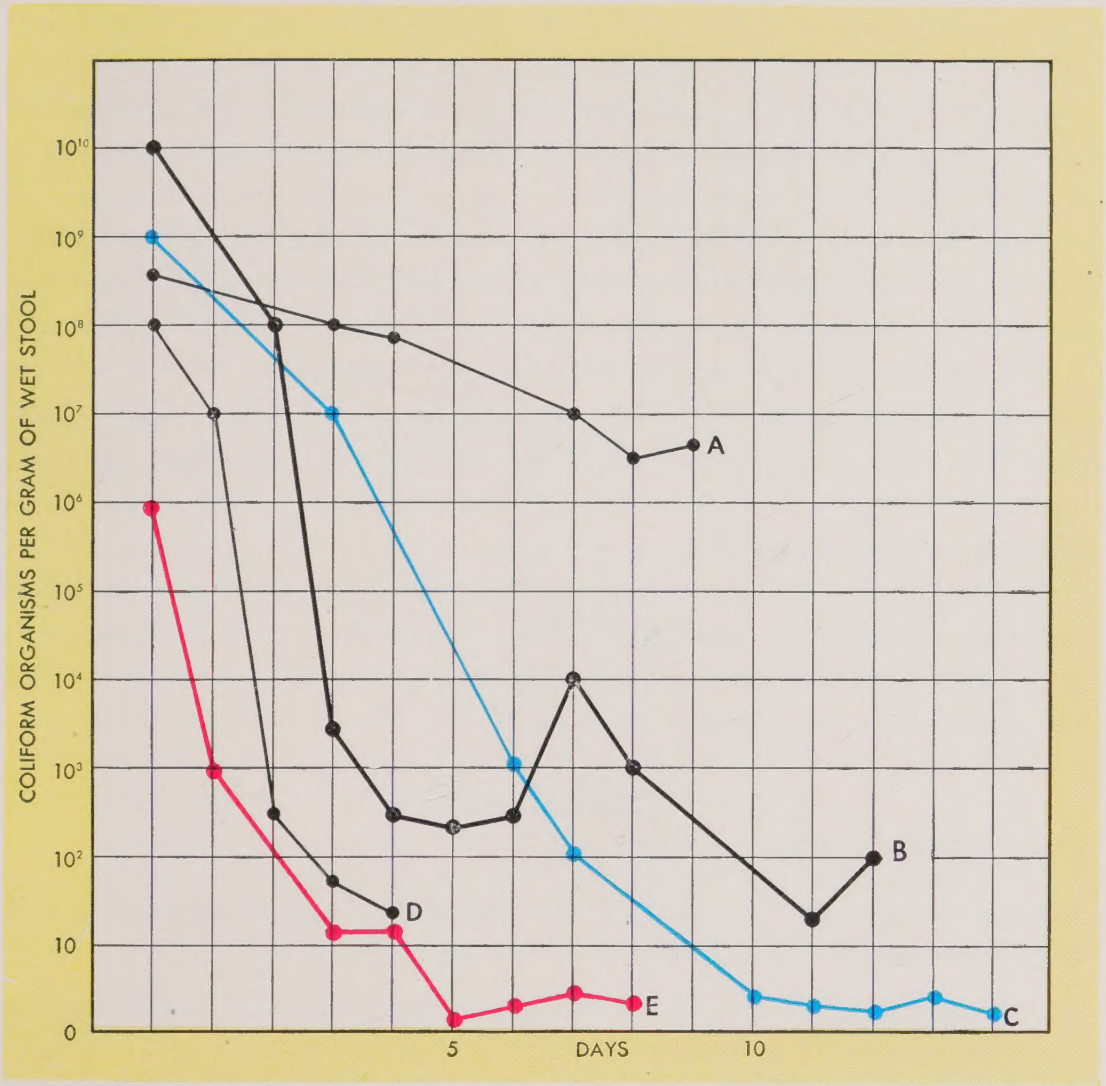
Indications: 'Sulfasuxidine' succinylsulfathiazole is the drug of choice for the treatment of *bacillary dysentery*. The drug is effective against the Shiga, Flexner and Sonne strains of the dysentery bacillus, and the response to treatment is prompt in both adults and children. Temperatures usually return to normal within from twenty-four to thirty-six hours. The drug has proved particularly



Carcinoma of the sigmoid colon; external view showing annular constriction.



Carcinoma of the sigmoid colon; bowel open to show internal aspects of growth.



The effect of varying dosages of succinylsulfathiazole on the coliform bacteria in the gastrointestinal tract of man. A shows the results of the oral administration of 0.1 Gm. per kilogram divided into six equal doses. B represents the effect of the similar administration of 0.2 Gm. per kilogram; C, the effect of 0.25 Gm. per kilogram; D, the effect of an initial dose of 0.25 Gm. per kilogram followed after four hours by 0.25 Gm. per kilogram per day in six equally divided doses (this patient had large ulcerating carcinoma of the rectum); E represents the course after the oral administration of three massive doses of 0.25 Gm. per kilogram at four hour intervals followed by 0.25 Gm. per kilogram per day divided into six equal quantities.

effective in eliminating dysentery bacilli from the stools of *carriers*.

'Sulfasuxidine' succinylsulfathiazole has been of great value in the *preoperative preparation* and *postoperative treatment* of *intestinal surgery* patients. Because the drug markedly alters the bacterial

flora, distention and gas pains are diminished, and the possibility of peritonitis and abscess formation is greatly reduced. The patient's convalescence is undisturbed and smooth. 'Sulfasuxidine' succinylsulfathiazole has proved effective also in the treatment of ulcerative colitis.

The drug has proved of value also in the treatment of *Escherichia coli infections* of the *genitourinary tract* that are refractory to other forms of therapy. Administration of the compound results in sterile urine in the great majority of patients.

Dosage: Initial dose, 0.25 Gm. per kilogram of body weight; maintenance dose, 0.25 Gm. per kilogram per day, divided into six equal portions and given at four hour intervals. See page 46 for detailed dosage schedule.

How Supplied: 'Sulfasuxidine' succinylsulfathiazole is supplied in 0.5-Gm. tablets in bottles of 100, 500 and 1,000, as well as in powder form (for oral administration) in ¼ and 1-pound bottles.

Abstracts

Dysentery

Vollum, R. L., and Wylie, J. A. H.: Control of Sonne Dysentery with Succinylsulphathiazole, Lancet *1*:91-92, Jan. 19, 1946.

Bacillary dysentery due to Shigella sonnei affected 33 of 70 boys in two schools. Ten received a daily dosage of 6 Gm. of succinylsulfathiazole for five days. All but one, a persistently heavy carrier, were negative for organisms two days after conclusion of therapy, but within four weeks 8 of the 10 boys were again excreting organisms. All patients in one of the schools were treated subsequently; ten days after completion of treatment all were negative and remained so for three months, except one who was positive on one occasion. Succinylsulfathiazole affords the best means of eradicating Sonne dysentery infection, providing the possibility of reinfection is reduced to a minimum.

Eisenoff, H. M., and Goldstein, H.: The Control of an Outbreak of Bacillary Dysentery with Sulfonamides, J. A. M. A. *123*:624-626, Nov. 6, 1943.

During an outbreak of Sonne dysentery in an orphanage, 83 bacteriologically positive patients and carriers were treated with four different sulfonamides. Twenty-seven children were given succinyl-

sulfathiazole in a dosage of 2 grains per pound of body weight. The illness was mild, the diarrhea lasting from two to four days; there were no deaths. The four sulfonamides appeared to be equally effective in controlling the disease. Complete inhibition of intestinal bacteria occurred for a time in 63 per cent of those treated with succinylsulfathiazole, 36 per cent of those treated with sulfaguanidine, 80 per cent of those treated with sulfathiazole, and 70 per cent of sulfadiazine-treated patients.

Roberts, T. L., and Daniels, W. B.: Succinylsulfathiazole in the Treatment of Bacillary Dysentery, J. A. M. A. *122*:651-653, July 3, 1943.

Eighty-nine patients with acute bacillary dysentery due to Shigella paradysenteriae were given 'Sulfasuxidine' succinylsulfathiazole until the temperature was normal and diarrhea absent for two days.

One hundred and thirty-six patients, who did not receive the drug, served as controls. Succinylsulfathiazole produced no amelioration of symptoms, nor was the course of the illness shortened, but this is not unusual in an illness lasting only four days.

However, this drug proved to have a significant effect on the carrier rate, which was 2.6 per cent in the treated group and 18.2 per cent in the control group.

Hardy, A. V., Burns, W., and DeCapito, T.: Studies of the Acute Diarrheal Diseases. Cultural Observations on the Relative Efficacy of Sulfonamides in Shigella Dysenteriae Infections, Pub. Health Rep. *58*:689-693, April 30, 1943.

Evaluation of sulfonamide treatment of bacillary dysentery revealed that, in general, succinylsulfathiazole was more effective than sulfaguanidine, and sulfadiazine was better than sulfathiazole. Succinylsulfathiazole and sulfaguanidine were less efficacious than sulfadiazine and sulfathiazole in Flexner Z infections, and the latter two gave better results in Schmitz infections.

Sulfadiazine gave the best results in control of massive Sonne infections, but succinylsulfathiazole was more effective in eliminating these organisms from convalescent and passive carriers. All four drugs had a significant effect on the course of the disease. Treated patients and carriers were rarely positive for as long as one week.

Smyth, C. J., Finkelstein, M. B., Gould, S. E., Koppa, T. M., and Leeder, F. S.: Acute Bacillary Dysentery (Flexner). Treatment with Sulfaguanidine and Succinylsulfathiazole, J. A. M. A. *121*:1325-1330, April 24, 1943.

A cure was effected in 12 (85 per cent) of patients with acute bacillary dysentery following treatment with succinylsulfathiazole in an initial dosage of 0.25 Gm. per kilogram of body weight, followed by 0.25 Gm. per kilogram daily for at least six successive days. Because this drug is relatively nontoxic, the amount of the original dose may be doubled if fever and diarrhea are not controlled after three days of therapy with the smaller doses. 'Sulfasuxidine' succinylsulfathiazole is believed to be the drug of choice in the treatment of this disease.

Dysentery Carriers

Painton, J. F., and Hantman, S.: An Outbreak of Sonne Dysentery, J. A M. A. *128*:1152-1155, Aug. 18, 1945.

'Sulfasuxidine' succinylsulfathiazole, in a daily dosage of 0.25 Gm. for seven days, proved to be effective in eradicating the carrier state during an outbreak of acute bacillary dysentery due to Bacterium sonnei. Among 71 patients treated a cure was obtained in 98.5 per cent. The disease was of relatively mild severity with active symptoms lasting only three to four days. Diarrhea was only moderately severe, subsiding after four to seven days with or without specific therapy. Fever was present in 75 per cent of the patients and lasted usually only two to four days.

Kuhns, D. M.: The Control of Endemic and Epidemic Diarrhea. Preliminary Report, South. M. J. *36*:393-401, June 1943.

During an outbreak of bacillary dysentery, 132 patients were treated with 'Sulfasuxidine' succinylsulfathiazole, 112 with sulfaguanidine, and 60 untreated patients were used as controls. Follow-up cultures by the swab method were made on 182 sulfonamide-treated patients at weekly intervals for three consecutive weeks, and on all the controls.

Both succinylsulfathiazole and sulfaguanidine were found to be effective in the treatment of convalescent carriers. All cultures taken from treated patients became negative during the follow-up period mentioned. Cultures from the 60 control cases were positive during a similar period following recovery from dysentery.

Surgery

Poth, E. J.: Sulfasuxidine* and Sulfathalidine,* Texas Rep. Biol. & Med. *4*:68-102, Spring 1946.

When 3.0 Gm. of succinylsulfathiazole are given every four hours preoperatively, the coliform organisms decrease to below 1,000 per gram of wet stool in 37 per cent of patients within 3 days, 80 per cent within five days, and 94 per cent in seven days. One bowel movement must be obtained daily. An enema consisting of 10 Gm. of sodium bicarbonate and 6 Gm. of succinylsulfathiazole may be given if necessary on the evening prior to operation. Preoperative and postoperative treatment with succinylsulfathiazole and phthalylsulfathiazole is especially valuable when the ureters are transplanted to empty into the rectosigmoid.

Bacon, H. E.: Evolution of Sphincter Muscle Preservation and Re-establishment of Continuity in the Operative Treatment of Rectal and Sigmoidal Cancer, Surg., Gynec. & Obst. *81*:113-127, Aug. 1945.

In the surgical treatment of 131 patients, of whom 102 underwent proctosigmoidectomy, 'Sulfasuxidine' succinylsulfathiazole was begun on the fifth preoperative day in an initial dosage of 0.5 Gm. per kilogram of body weight followed by 0.25 Gm. per kilogram every four hours. Administration of the drug was resumed usually on the third or fourth postoperative day in the same dosage. Fluids, a low residue diet, blood transfusions and supplementary vitamins play an important part in preoperative preparation. Following operation glucose-saline solution, and whole blood if necessary, are transfused. Careful attention is paid to hydration, acid-base balance, nitrogen balance and blood protein levels.

Newton, F. C., and Blodgett, J. B.: Succinylsulfathiazole and Intestinal Suction in Surgery of the Large Bowel, Surgery *18*:200-206, Aug. 1945.

Preoperative administration of succinylsulfathiazole and the use of intestinal suction both before and after operation were employed as adjuncts in the treatment of 36 patients in a series of 114 undergoing large bowel resection. The gross incidence of complications decreased from 58 to 25 per cent and the gross mortality rate from

*See footnote page 7.

19 to 3 per cent in this test group of 36 cases, and the Mikulicz operation was not required. When similar operative procedures (resections and anastomoses) in the two groups were compared, postoperative infection was reduced from 43 to 6 per cent, and the mortality rate decreased from 22 to 3 per cent.

Behrend, M.: Colon Surgery and the Sulfonamide Drugs with Especial Reference to the Elimination of the Mikulicz Operation, J. A. M. A. *128*:9-12, May 5, 1945.

Succinylsulfathiazole is of great value in the preoperative preparation of patients undergoing surgery of the intestine for cancer or other lesions. The dosage employed is 0.25 Gm. per kilogram of body weight for at least one week before operation. Colonic irrigations are not required, since the drug reduces the bowel contents and renders it almost empty. The decrease of bacterial flora to a minimum makes it possible to perform a one stage operation in place of the multiple stage operation, thus subjecting the patient to less surgery and shortening the convalescent period.

Archer, H. L., and Lehman, E. P.: Clinical and Laboratory Experiences with Succinylsulfathiazole, Ann. Surg. *119*:518-525, April 1944.

Succinylsulfathiazole was given preoperatively to 36 patients in whom the large bowel was divided or anastomosed at the primary operation. Three patients died (8.3 per cent); in only one case could death possibly have been attributed to failure of the drug, giving a corrected mortality rate of 2.8 per cent. Only two abdominal wounds were infected; in the entire group there was no clinical evidence of acute local or general peritonitis, and acute local peritonitis was found at postmortem examination in only one case. Succinylsulfathiazole is an effective adjuvant in surgical treatment, since it frequently obviates multiple stage procedures and the diminution of intestinal bacteria makes it possible to employ a balanced preoperative diet.

Behrend, M.: Succinylsulfathiazole (Sulfasuxidine) and the Elimination of the Mikulicz Operation, Surg. Clin. North America *24*:238-247, Feb. 1944.

As a result of preoperative preparation of the patient with succinyl-

sulfathiazole, the colon is practically empty at the time of operation, and it is possible to perform a single stage resection with end to end anastomosis, instead of a multiple stage Mikulicz. Glucose and blood transfusions are given immediately after operation, and succinylsulfathiazole is continued for four or five days. The success of all surgery of the colon depends on the preoperative and postoperative care of the patient. This includes primary purge, liquid diet, colonic irrigations, and parenteral fluids including glucose, amino acids, plasma and blood transfusions.

Urinary Infections

Poth, E. J.: Sulfasuxidine* and Sulfathalidine,* Texas Rep. Biol. & Med. *4*:68-102, Spring 1946.

'Sulfasuxidine' succinylsulfathiazole is of value in the treatment of Escherichia coli infections of the urinary tract. In one patient who failed to respond to therapy with other sulfonamides, the urine became sterile within the third and ninth days following administration of succinylsulfathiazole in a daily dosage of 0.25 Gm. given every four hours. The coliform count in the feces decreased from 108 to less than 10 organisms per gram, and thus a constant source of reinfection of the urinary tract probably was removed.

Everett, H. S., Scott, R. B., and Steptoe, P. P., Jr.: The Treatment of Urinary Infections with 'Sulfasuxidine' Succinylsulfathiazole, Am. J. Obst. & Gynec. *49*:114-127, Jan. 1945.

A number of patients with urinary tract infections due to Escherichia coli, which are refractory to other forms of therapy, showed prompt therapeutic response to the administration of 'Sulfasuxidine' succinylsulfathiazole. The majority of patients received 0.25 Gm. per kilogram of body weight for one week. One-half of this daily dosage then was administered for an additional one or two weeks. The urine of approximately 90 per cent of 34 patients became sterile as a result of treatment, and follow-up studies for from three to twenty months showed a recurrence of infection in only three individuals.

*See footnote page 7.

Ulcerative Colitis

Borland, J. L.: Treatment of Some Common Infections of the Bowel with Sulfonamide Drugs, South. M. J. *39*:285-289, April 1946.

'Sulfasuxidine' succinylsulfathiazole was employed in the treatment of two patients with chronic ulcerative colitis in an attempt to check the progress of the disease and to induce a remission. The preliminary step was to control the diarrhea and bleeding and to bring the bowel back to normal by the administration of sulfadiazine. One patient remained free of symptoms, with no evidence of mucosal inflammation or bleeding, for four months on a daily dosage of 4 Gm. of succinylsulfathiazole. The second patient remained normal for one month, at which time the drug was discontinued. The return of symptoms a month later necessitated a second course of sulfadiazine.

Pollard, H. M.: The Clinical Use of Succinylsulfathiazole in Chronic Ulcerative Colitis, Gastroenterology *4*:4-8, Jan. 1945.

Administration of succinylsulfathiazole in a dosage usually of 12 Gm. daily for two or three weeks produced a clinical response in 77 per cent of 36 patients with chronic ulcerative colitis. In several cases an elevated temperature of one to three months' duration was reduced to normal forty-eight hours after therapy was begun. A decrease in number of daily stools, improvement in appetite, and gain in weight occurred in a number of patients. Although the bowel is not sterilized, it is believed that the intestinal bacteria are altered sufficiently by the drug to return the bowel to a more normal physiologic state.

Crohn, B. B.: The Clinical Use of Succinyl Sulfathiazole (Sulfasuxidine*), Gastroenterology *1*:140-146, Feb. 1943.

Of 28 patients with ulcerative colitis (nonspecific) treated with 'Sulfasuxidine' succinylsulfathiazole, a cure was effected in 5, and 11 showed improvement. No response was elicited in 10 patients, and in 2 toxic reactions necessitated discontinuance of the drug. The dosage was 0.25 Gm. per kilogram of body weight for ten days, followed by a second series after a lapse of five days. Recognition

*See footnote page 7.

of the disease in its early stage and intensive therapy with succinylsulfathiazole may produce encouraging results, not only in inducing a remission but in preventing recurrences.

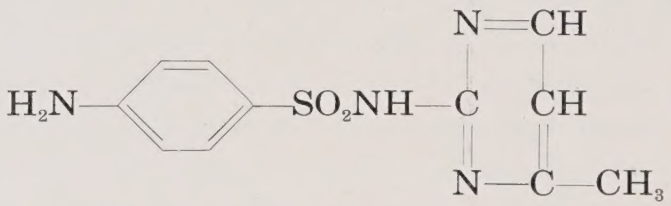
Streicher, M. H.: Sulfonamides: Clinical Evaluation in Infectious Diseases of the Colon, M. Clin. North America *27*:189-194, Jan. 1943.

In a comparison of the results obtained in the treatment of ulcerative colitis with various sulfonamides, 'Sulfasuxidine' succinylsulfathiazole was found to be the most effective and the least toxic. Seven of 8 patients with acute ulcerative colitis showed remarkable progress, and 8 of 10 patients with chronic ulcerative colitis also responded. Improvement occurred within a relatively short time, and included relief from abdominal pain, decrease in amount or complete disappearance of blood and pus in the stools, and a decrease in the number of stools. A considerable diminution of the bacterial count was obtained with succinylsulfathiazole.

'Sulfasuxidine' succinylsulfathiazole crystals precipitated from distilled water for purposes of identification and comparison. The possibility of such crystals appearing in urine is remote because of this compound's very slight absorption from the gastrointestinal tract and great solubility in urine.

Sulfamerazine

Formula: Sulfamerazine (4-methyl-2-sulfanilamidopyrimidine) is a monomethyl derivative of sulfapyrimidine (sulfadiazine). A development of the Medical Research Laboratories of Sharp & Dohme, it is represented by the structural formula



Sulfamerazine is a white, crystalline powder, poorly soluble in water and the common organic solvents. It is readily soluble in dilute acids and dilute alkalies, and may be converted into the sodium salt which is soluble in water.

Characteristics: Sulfamerazine is regarded clinically as the systemic sulfonamide of smaller dosage. This compound is unique in that it combats systemic infections with approximately one-half the usual total dosage of sulfadiazine or sulfathiazole.

Administered orally, sulfamerazine is characterized by rapid absorption, which minimizes the necessity of intravenous therapy. It is more completely absorbed from the gastrointestinal tract than other systemic sulfonamides and thus results in higher blood levels. Because the compound is more slowly eliminated by the kidneys, smaller or less frequent doses produce and maintain therapeutic concentrations of the drug in the blood and tissues.

Sulfamerazine is considerably less toxic than sulfathiazole and slightly less toxic than sulfadiazine. Renal injury and formation of drug concretions are less likely to occur with sulfamerazine because of the greater solubility of both the free and conjugated drug

in acid and neutral urine, and because of smaller dosage.

Indications: Sulfamerazine is indicated in treatment of *beta hemolytic streptococcic* infections such as tonsillitis, pharyngitis, peritonsillar abscess, acute sinusitis, otitis media, mastoiditis, adenitis, cellulitis, pneumonia, empyema, peritonitis, erysipelas and scarlet fever; *pneumococcic infections* such as pneumonia, otitis media, mastoiditis, sinusitis and empyema. The compound also is indicated in the treatment of *meningococcic meningitis, gonorrhea, impetigo* and *Friedländer bacillus infections.*

Possible *prophylactic* uses include susceptible scarlet fever contacts, otitis media, peritonitis, susceptible meningococcic meningitis contacts, treatment of meningococcic carriers, secondary infection or complications subsequent to influenza, infectious gangrene, rheumatic fever and gonorrhea.

Dosage: An adequate therapeutic blood level of from 10 to 15 mg. of sulfamerazine per 100 cc. of blood should be maintained. See page 46 for detailed dosage schedule.

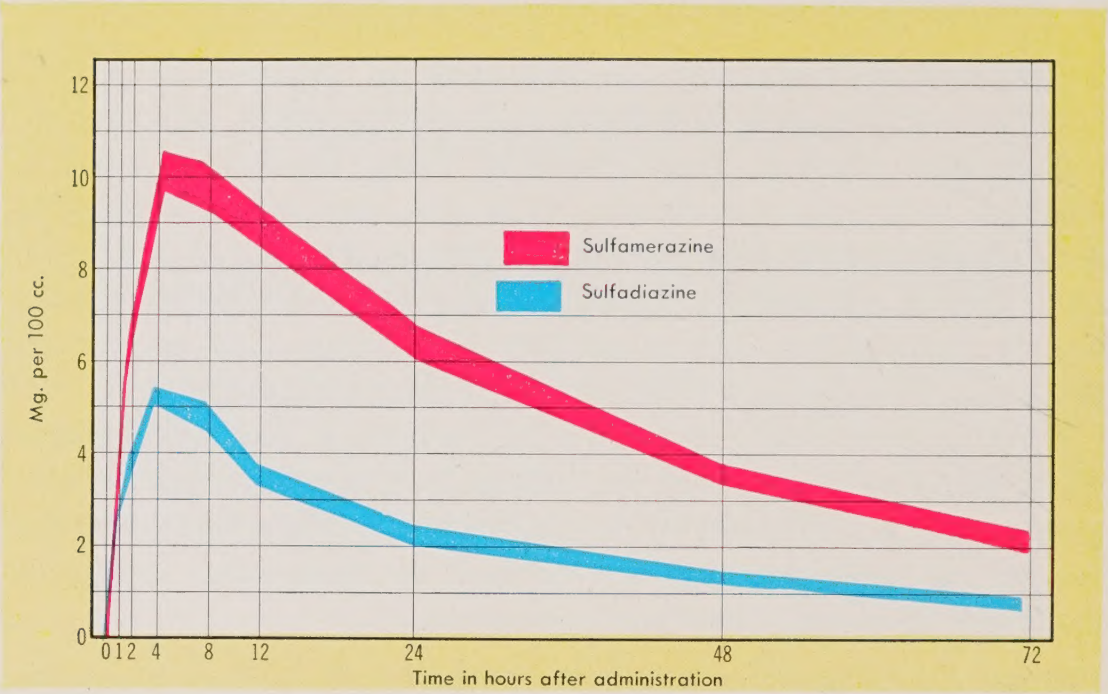
How Supplied: Sulfamerazine is supplied in 0.5-Gm. tablets, for oral administration, in bottles of 100, 500 and 1,000; also in ¼-pound packages of powder. Sodium Sulfamerazine, for intravenous administration, is supplied in 5-Gm. vials of sterile powder and in 50-cc. ampuls of a 6% solution. Sulfamerazine chemical reagent is supplied in 1-Gm. vials.

Abstracts

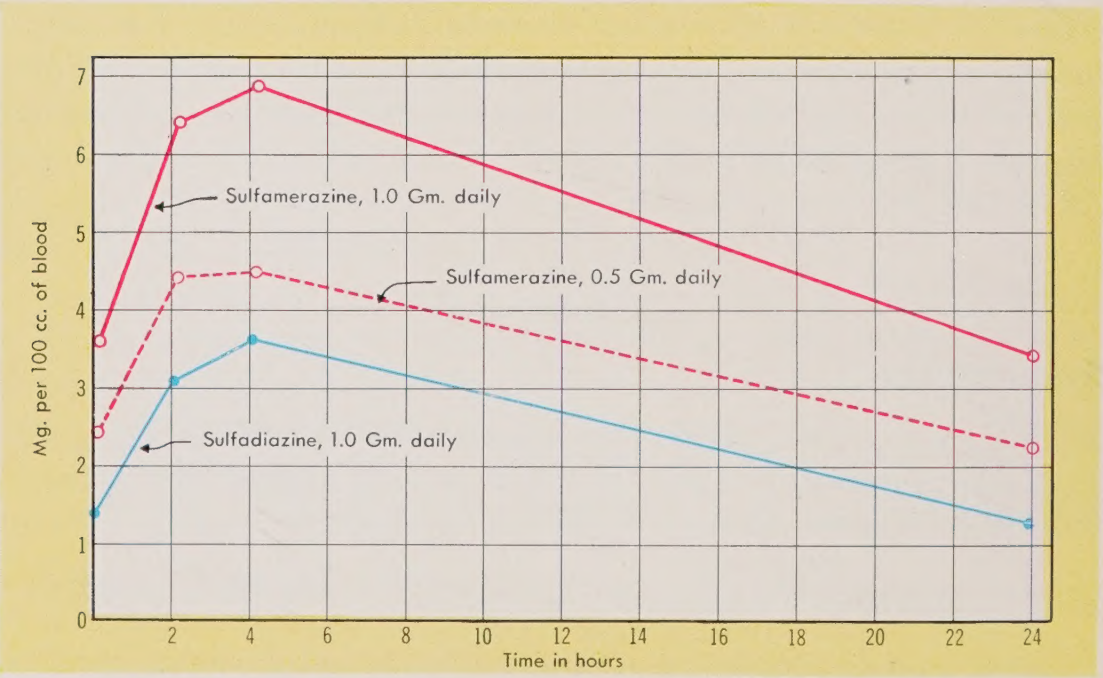
Pneumonia

Genecin, A., Austrian, R. C., and Nelson, R. A.: Sulfamerazine in the Treatment of Pneumococcal Lobar Pneumonia. An Analysis of 292 Cases, Bull. Johns Hopkins Hosp. 76:112-133, March 1945.

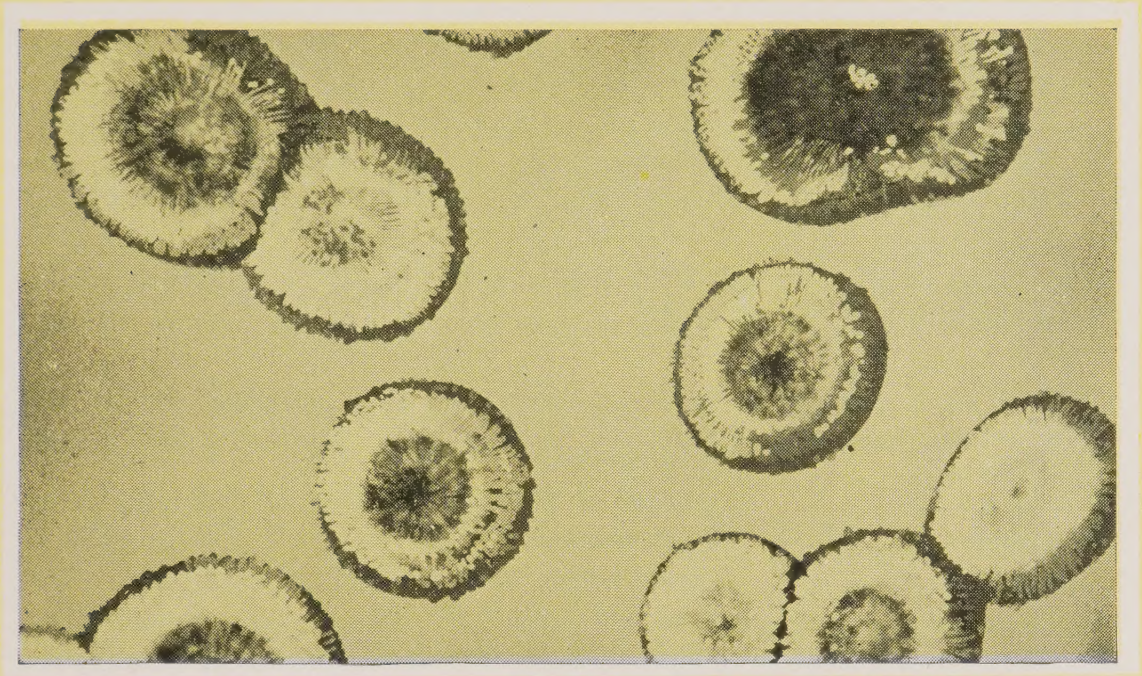
In a group of 256 patients with pneumonia treated with sulfamerazine alone, the fatality rate of 5.4 per cent indicated that this drug is at least as effective as other sulfonamides in the therapy of this disease. Although the mortality rates in the two groups receiving supplementary treatment with serum or penicillin were relatively



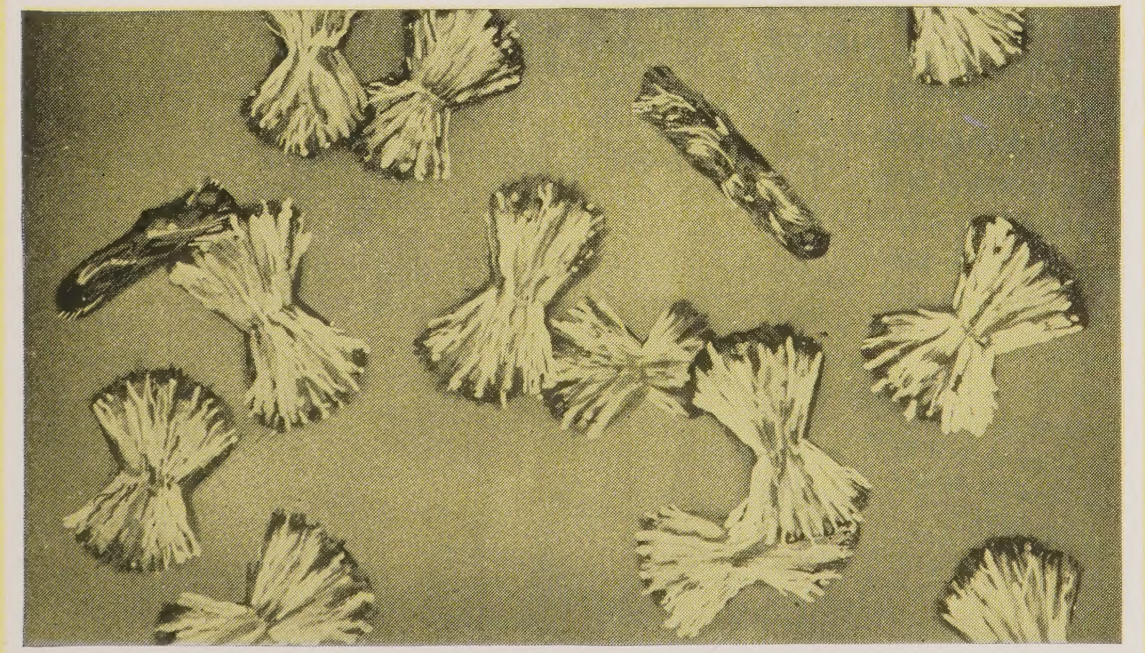
Average concentration of sulfonamides in the blood of 14 normal men following single oral doses of 0.05 Gm. per kilogram of sulfadiazine and sulfamerazine at an interval of one week. In each curve the lower line indicates the concentration of free sulfonamide and the upper line the concentration of total sulfonamide in the blood.



Average daily sulfonamide concentration in the blood of 9 normal males, receiving, each day, single oral doses of sulfadiazine, 1.0 Gm., sulfamerazine, 0.5 Gm., or sulfamerazine, 1.0 Gm.



Photomicrograph of sulfamerazine crystallized from the urine of a human subject receiving the drug. Crystal-free urine was heated with pure sulfamerazine; the crystals were obtained on cooling.



Photomicrograph of acetylsulfamerazine crystallized from the urine of a human subject receiving sulfamerazine. Crystal-free urine was heated with pure acetylated drug; the crystals were obtained on cooling.

high (38.4 per cent and 27.3 per cent respectively), these patients were critically ill, and the incidences of involvement of more than one lobe, of concurrent disease, complications and bacteriemia were relatively high. The mortality rate in the entire series of 292 patients was 8.9 per cent and the incidence of nonfatal complications 15.4 per cent. When the deaths occurring within twenty-four hours after admission to hospital were excluded, the case fatality rate was reduced to 4.0 per cent.

Volini, I. F., Engbring, G. M., Schorsch, H. A.: Sulfamerazine. A Clinical Study of 200 Pneumonia Patients, Illinois M. J. *87*:13-19, Jan. 1945.

Sulfamerazine was employed in the treatment of 200 patients with pneumonia due to the pneumococcus (45 per cent, Streptococcus viridans, Klebsiella pneumoniae, and the staphylococcus; in 78 cases the etiology was not determined. The corrected mortality rate, eliminating cases fatal within twenty-four hours of admission, was 9.5 per cent for the entire series. The temperature returned to normal in 65 per cent of the 200 patients within 72 hours. Clinical results were similar to those obtained with sulfadiazine although toxic reactions were fewer and the complications of pneumonia, especially empyema, were observed less often.

Flippin, H. F., Reinhold, J. G., and Gefter, W. I.: Sulfamerazine: Clinical Evaluation in 400 Cases, M. Clin. North America *27*:1447-1462, Nov. 1943.

Sulfamerazine was administered to 199 patients with pneumococcic pneumonia, in 34 (17 per cent) of whom positive blood cultures were obtained. The mortality rate for the entire group was 6.5 per cent. Successfully treated patients received an average of 22.9 Gm. of sulfamerazine over an average period of 6.4 days. The clinical response of 15 patients with primary atypical pneumonia was not so striking as that observed in the bacterial pneumonia, but all patients recovered with no secondary complications. Ten of 11 patients with bronchopneumonia in which a specific causative organism was not identified recovered following therapy.

Hall, W. H., and Spink, W. W.: Sulfamerazine—Clinical Evaluation in 116 Cases, J. A. M. A. *123*:125-131, Sept. 18, 1943.

Sulfamerazine was compared with sulfadiazine, in a series of 116 patients having a variety of infections, with respect to pharmacology, therapeutic effectiveness and toxicity. Results in 40 cases of

pneumococcic pneumonia or bronchitis showed that sulfamerazine is as effective as sulfadiazine. Adequate blood concentrations could be maintained with smaller, less frequent doses of sulfamerazine than of sulfadiazine. Sulfamerazine also caused a more abrupt fall in temperature in patients with pneumonia. Toxic reactions occurred no more frequently with sulfamerazine than with sulfadiazine. Adequate fluid intake and alkalization of the urine may prevent urinary complications during administration of sulfamerazine and sulfadiazine.

Flippin, H. F., Gefter, W. I., Domm, A. H., and Clark, J. H.: Studies on 2-Sulfanilamido-4-Methylpyrimidine (Sulfamerazine, Sulfamethyldiazine) in Man: The Treatment of Pneumococcic Pneumonia, Am. J. M. Sc. *206*:216-221, Aug. 1943.

Sulfamerazine was administered to 80 patients with pneumonia and sulfadiazine was given to a similar number. The mortality rate was 7.5 per cent in the sulfamerazine treated group as compared with 10 per cent in the sulfadiazine group. Clinical response, as manifested by a fall in temperature, occurred somewhat more rapidly with sulfamerazine than with sulfadiazine, possibly due to the higher and more rapidly attained blood concentrations in the case of the former. Within seventy-two hours the temperature returned to normal in 72.9 per cent of patients receiving sulfamerazine and in 59.8 per cent of patients to whom sulfadiazine was administered.

Meningitis

Forbes, G. B., Perley, A., and Dehlinger, J.: The Use of Sulfamerazine in Infants and Children, J. Pediat. *28*:24-36, Jan. 1946.

To obtain optimal blood concentrations while treating patients with meningococcic meningitis, sodium sulfamerazine was administered subcutaneously in an initial dose of 60 cc. of 0.5 per cent solution per kilogram of body weight and subsequently doses of 20 cc. per kilogram every eight hours. After two days 0.1 Gm. of sulfamerazine per kilogram was given orally every eight hours, and this dosage was halved when infection was under control. Parenteral administration was continued for longer periods without untoward effects in meningitis due to the pneumococcus, hemolytic streptococcus or influenza bacillus. Prompt response to sulfamerazine treatment occurred in all 17 cases of acute meningococcic meningitis and also in pneumococcic and influenzal meningitis.

Reinhold, J. G., Flippin, H. F., Zimmerman, J. J., Gefter, W. I., and Riddler, J. G.: The Relationship Between Concentration of Sulfamerazine in Body Fluids and the Response in Treatment of Meningococcic Meningitis, J. Clin. Investigation *24*:352-361, May 1945.

The response of meningococcic meningitis to sulfamerazine therapy was evaluated in 188 patients. In the presence of higher concentrations of sulfamerazine in the body fluids the patient's temperature fell more rapidly than with lower concentrations. The average time required for return to normal temperature was shortened one day by each increment of 1 mg. per 100 cc. in the serum sulfamerazine concentration. Meningitic irritation disappeared more quickly in patients who exhibited higher concentrations of plasma sulfamerazine. Maintenance of 20 mg. or more per 100 cc. of plasma should give more rapid therapeutic responses, and the increased incidence of toxic reactions should be offset to some extent by the decreased duration of therapy.

Oliver, C. S., and Anderson, D. G.: The Treatment of Meningococcic Meningitis with Sulfamerazine, Am. J. M. Sc. *208*:597-602, Nov. 1944.

Fifty-six patients presenting the typical clinical picture of meningitis, which was confirmed as meningococcic meningitis by bacteriologic study, were treated with sulfamerazine. The average duration of therapy was 8.4 days. The average total dosage of sulfamerazine was 24.8 Gm. for adults and 16.6 Gm. for children. Thirty-five patients (62 per cent) showed clinical improvement, usually evidenced by return of consciousness and mental clarity, within twenty-four to forty-eight hours. The average duration of fever was six days. No deaths occurred in this series of 56 patients, and it is concluded that sulfamerazine is an effective agent in the treatment of meningococcic meningitis.

Flippin, H. F., Reinhold, J. G., and Gefter, W. I.: Sulfamerazine: Clinical Evaluation in 400 Cases, M. Clin. North America *27*:1447-1462, Nov. 1943.

The treatment of 12 patients with pneumococcic meningitis resulted in a mortality rate of 83 per cent, which was believed to be similar to that observed in unselected cases treated by other methods. Of the fatal cases, 2 were moribund on admission, 2 were complicated by pneumonia, and endocarditis developed in another. In a series of 99 patients with meningococcic meningitis the mortality rate was 5 per cent as compared with that of 12.5 per cent reported for a similar series treated with sulfadiazine. Three of 5 patients with influenzal meningitis recovered with sulfamerazine therapy.

Lepper, M. H., Sweet, L. K., and Dowling, H. F.: The Treatment of Meningococcic Infections with Sulfadiazine and Sulfamerazine (Sulfamethyldiazine, Monomethylsulfadiazine), J. A. M. A. *123*:134-138, Sept. 18, 1943.

Among 118 meningococcic meningitis patients treated with either sulfamerazine or sulfadiazine, an overall mortality rate of 10.2 per cent was observed. The respective death rates for the two drugs were almost identical. Prognosis was influenced to the greatest degree by the presence of coma on admission and by the age of the patient. Twenty-five per cent of those in coma on admission and almost 25 per cent of patients over 40 years of age died. The mortality rate with sulfonamide therapy remained constant in spite of the increase in incidence and severity of the disease in epidemic periods.

Gefter, W. I., Rose, S. B., Domm, A. H., and Flippin, H. F.: Studies on 2-Sulfanilamido-4-Methylpyrimidine (Sulfamerazine, Sulfamethyldiazine) in Man: The Treatment of Meningococcic Meningitis, Am. J. M. Sc. *206*:211-216, Aug. 1943.

Active sulfamerazine treatment of 45 patients with meningococcic meningitis averaged 9.5 days for adults and 8.6 days for children. The average total dosage for adults was 56.4 Gm. and for children 19.3 Gm. Definite clinical improvement was apparent within forty-eight hours. Fever persisted for an average of five days following the initial therapeutic response. Complications of the disease were observed in 8 patients, but all were transient and recovery was complete. The mortality rate of 6.7 per cent using sulfamerazine is compared with a rate of 57.5 per cent in a series of patients observed during 1935, 1936 and 1937 and with 40 per cent in a group reported in 1942.

Pneumococcic, Streptococcic, Meningococcic and Other Infections

Forbes, G. B., Perley, A., and Dehlinger, J.: The Use of Sulfamerazine in Infants and Children, J. Pediat. *28*:24-36, Jan. 1946.

The therapeutic effectiveness of sulfamerazine was evaluated in 135 children and infants hospitalized for various types of infections. Satisfactory clinical results were obtained in patients with acute peritonitis due to Escherichia coli, streptococcic tonsillitis and laryngitis, lobar pneumonia, bronchopneumonia in small infants, severe bronchitis, erysipelas, acute pyelitis due to E. coli, cellulitis of the thigh

accompanied by femoral adenitis, and exfoliative dermatitis of the newborn. In pediatric patients the use of sulfamerazine orally and sodium sulfamerazine subcutaneously, in three-fourths of the dosage required with other sulfonamides, yielded therapeutic results comparable to those obtained with sulfapyrazine, sulfadiazine and sulfathiazole.

Kittredge, W. E., and Butt, A. J.: Sulfamerazine in the Treatment of Genito-Urinary Infections. An Analysis of 151 Consecutive Cases, New Orleans M. & S. J. *98*:63-65, Aug. 1945.

The clinical application of sulfamerazine in genito-urinary infections was investigated in 151 patients, including 137 cases of urinary infection, 7 of gonorrheal urethritis and 7 of nonspecific urethritis. A cure was effected in 85 per cent of bacillary cases, 89 per cent of staphylococcic cases, and 61 per cent of cases with mixed infection. Sulfamerazine had no effect on the Proteus bacillus infection; it cured only 2 of 7 patients with gonorrheal urethritis and 2 of 7 cases of nonspecific urethritis. A number of patients responded to treatment with sulfamerazine after previous therapy with other agents had failed.

Flippin, H. F., Reinhold, J. G., and Gefter, W. I.: Sulfamerazine: Clinical Evaluation in 400 Cases. M. Clin. North America *27*:1447-1462, Nov. 1943

Fifteen hemolytic streptococcic infections were treated with sulfamerazine with good results except for one case in which an acute endocarditis due to Streptococcus hemolyticus supervened. Recovery, with no relapses, followed administration of the drug to 10 male patients with gonococcic urethritis. There was striking clinical improvement after administration of sulfamerazine in 3 patients with benign lymphocytic choriomeningitis and in 2 with acute encephalitis. Clinical results in 11 patients suffering from a variety of genito-urinary tract infections were satisfactory. Escherichia coli alone, or accompanied by other organisms, was recovered from the urine of 7 of these patients.

Hageman, P. O., Harford, C. G., Sobin, S. S., and Ahrens, R. E.: Sulfamerazine. A Clinical Study of Its Pharmacodynamics, Therapeutic Value and Toxicity, J. A. M. A. *123*:325-330, Oct. 9, 1943.

Therapeutic results comparable to those observed with sulfadiazine were obtained following sulfamerazine therapy of meningococcic and pneumococcic infections. Miscellaneous infections in which the

gonococcus or staphylococcus was the causative organism responded similarly.

Good to excellent therapeutic results were obtained also with sulfamerazine therapy of a number of beta hemolytic streptococcus infections, including pharyngitis, tonsillitis, peritonsillar abscess, erysipelas and scarlet fever, and in several cases of pyelitis and cystitis due to Escherichia coli.

Hall, W. H., and Spink, W. W.: Sulfamerazine—Clinical Evaluation in 116 Cases, J. A. M. A. *123*: 125-131, Sept. 18, 1943.

Of 116 patients treated with sulfamerazine, 47 were ill with pneumonia, 31 with streptococcic sepsis, 11 with staphylococcic sepsis, 8 with pneumococcic bronchitis, 3 with meningococcic meningitis, 2 with influenzal meningitis (type B), 2 with streptococcic meningitis and 12 with miscellaneous infections.

Sulfamerazine appeared to be as effective as sulfadiazine in 33 cases of streptococcic infection, but was less successful than sulfathiazole in the treatment of staphylococcic sepsis. The 2 patients with influenzal meningitis and the 3 patients with meningococcic meningitis responded well to therapy with sulfamerazine.

Rheumatic Fever Prophylaxis

Rosenberg, E. F., and Hench, P. S.: Recent Advances in the Treatment of Rheumatic Fever; with Special Reference to Sulfonamide Prophylaxis and Intravenous Salicylate Therapy, M. Clin. North America *30*:489-509, May 1946.

The sulfonamides are of definite value for prevention of the recurrences that often follow hemolytic streptococcic infections, otitis media, scarlet fever and erysipelas. Treatment is carried out either in the fall and winter months or throughout the year.

The daily dosage usually is 0.5 to 1 Gm. of sulfonamide for children and 1 to 2 Gm. for adults. Sulfanilamide, sulfathiazole and sulfadiazine have been employed, but sulfamerazine appears to be preferable, since effective blood levels may be maintained by administration of a single small daily dose.

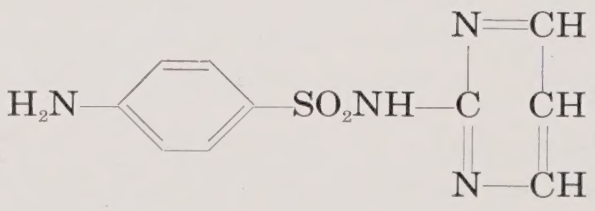
More extensive use of sulfamerazine may reduce still further the chances of significant toxicity due to the use of sulfonamides.

Hansen, A. E.: Rheumatic Recrudescences: Diagnosis and Prevention, J. Pediat. *28*:296-308, March 1946.

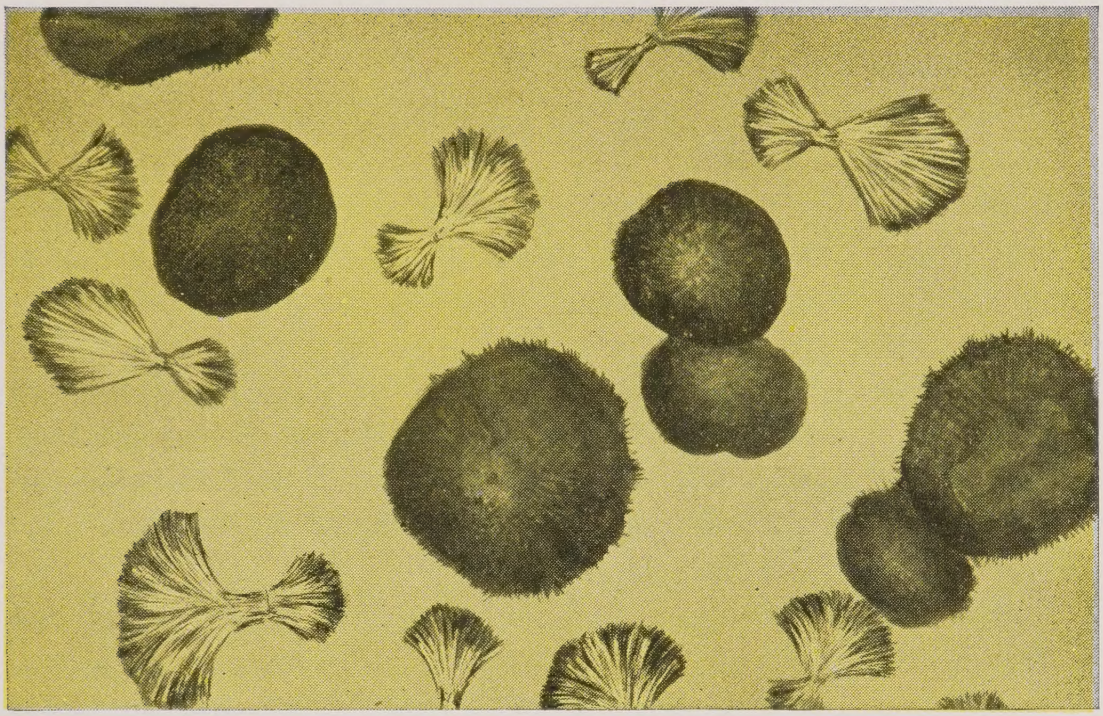
The prevention of hemolytic streptococcus infections and recrudescences of rheumatic infection is an important factor in the management of this disease, since the mortality rate appears to be directly related to the number of flare-ups of this condition. A summary of studies by a number of investigators reveals an incidence of recurrences of 1.5 per cent for the group treated prophylactically with sulfonamides in contrast to 19 per cent for the untreated group. The dosage of sulfamerazine or sulfadiazine should be 1.0 Gm. daily for children over 9 or 10 years of age, and 0.5 Gm. daily for children under this age. Sulfonamide prophylaxis should be carried out for at least five years after the initial attack or until the patient is approximately 17 years old.

Sulfadiazine

Formula: Sulfadiazine—2-(p-aminobenzenesulfonamido)-pyrimidine—is one of a group of heterocyclic derivatives of sulfanilamide. A development of the Medical Research Laboratories of Sharp & Dohme, it is represented by the structural formula



Sulfadiazine is a white, odorless, crystalline powder, sparingly soluble in water and insoluble in ether and chloroform. It is readily soluble in alkalies and mineral acids.



Sulfadiazine, because of its relatively lower solubility, may appear in the urine as well as the acetylated derivative. Free sulfadiazine forms dark, dense, greenish globules with either fuzzy or clean edges. Acetylsulfadiazine crystals form "shocks of wheat" with eccentric binding. The eccentric binding differentiates it from the central binding of acetylsulfathiazole crystals.

Characteristics: Sulfadiazine is a widely used systemic sulfonamide. It is absorbed more slowly from the gastrointestinal tract than sulfathiazole and sulfamerazine. It is eliminated by the kidneys more slowly than sulfathiazole but more rapidly than sulfamerazine. Thus the compound maintains high blood levels longer than sulfathiazole but not as long as sulfamerazine.

In general, sulfadiazine therapy has been characterized clinically by the following advantages: reduced occurrence of nausea or vomiting; high blood concentrations readily attained after oral dosage; low proportion of acetylated sulfadiazine in the blood; gradual decline of sulfadiazine blood levels after discontinuance of the drug; ready penetration into ascitic or pleural fluids, and

cerebrospinal fluid; and greater solubility of acetylsulfadiazine in urine than that of sulfadiazine itself.

Sulfadiazine is less toxic than sulfathiazole but slightly more toxic than sulfamerazine.

Indications: Sulfadiazine is indicated in treatment of *beta hemolytic streptococcic infections* such as tonsillitis and pharyngitis, peritonsillar abscess, acute sinusitis, otitis media, mastoiditis, adenitis, cellulitis, pneumonia, empyema, peritonitis, erysipelas and scarlet fever; *pneumococcic infections* such as pneumonia, otitis media, mastoiditis, sinusitis and empyema. Sulfadiazine also is indicated in the treatment of *meningococcic meningitis*, *gonorrhea*, *osteomyelitis*, *impetigo*, *Friedländer bacillus infections* and *staphylococcic infections* such as sepsis and pneumonia.

Possible *prophylactic* uses include susceptible scarlet fever contacts, otitis media, peritonitis, and prevention of infection in burns.

Dosage: Initial oral dose for adults is 4 Gm. This is followed by a maintenance dose of 1 Gm. every four hours, until temperature, pulse rate and respiration have been essentially normal for a period of 72 hours. See page 47 for detailed dosage schedule.

How Supplied: Sulfadiazine U. S. P. is supplied in 0.5-Gm. tablets, for oral administration, in bottles of 100 and 1,000. Sodium Sulfadiazine, for intravenous administration, is supplied in 5-Gm. vials of sterile powder and in 50-cc. ampuls of a 5% solution.

Abstracts

Pneumonia

Shackman, N. H., and Bullowa, J. G. M.: Sulfadiazine Administration Alone and with Antipneumococcus Serum in Treatment of Pneumococcic Pneumonia, Arch. Int. Med. 72:329-345, Sept. 1943.

A series of 232 patients with pneumococcic pneumonia were treated with sulfadiazine. Another 70 patients received antipneumococcic serum in addition to sulfadiazine. The mortality rate was slightly higher among those receiving the combined treatment, but this probably was due to the inclusion of more severely ill patients in

this group. In no instance were reactions such as nausea or vomiting severe enough to require discontinuance of the drug. The authors concluded that sulfadiazine is as effective as sulfapyridine in the treatment of pneumococcic pneumonia.

Dowling, H. F., Hartman, C. R., Feldman, H. A., and Jenkins, F. A.: Comparative Value of High and Low Doses of Sulfadiazine in the Treatment of Pneumococcic Pneumonia, Am. J. M. Sc. *205*:197-203, Feb. 1943.

Among 160 patients with pneumococcic pneumonia, the mortality rate, excluding deaths due to complicating diseases, was 4.4 per cent following sulfadiazine therapy. Eighty-one patients received 2 Gm. followed by 0.5 Gm. every four hours, and 79 were given 6 Gm. followed by 1 Gm. every four hours. There was little difference in number of deaths in the two groups (3 and 4 respectively). The temperature fell slightly more rapidly on the higher dosage, and hospitalization lasted for an average of 3.4 days less. Relapse, spread of infection to another lobe and slow resolution were observed less than half as frequently in the high dosage group.

Meningococcic Infections

Appelbaum, E.: Sulfadiazine and Its Sodium Compound in Treatment of Meningococcic Meningitis and Meningococcemia, Am. J. M. Sc. *207*:492-507, April 1944.

Excellent results were obtained in the treatment of 141 patients with meningococcic meningitis and 8 with meningococcemia not involving the meninges, employing sulfadiazine orally and sodium sulfadiazine intravenously. Adequate therapy required a blood level of 10 to 15 mg. of sulfadiazine per 100 cc., and a cerebrospinal fluid concentration of 7 to 10 mg. per 100 cc. Clinical improvement was rapid, a sharp fall in temperature occurring on the second or third day of therapy. Only 2 meningitis patients died, a mortality rate of 1.4 per cent, and all patients with meningococcemia recovered.

Marangoni, B. A., and D'Agati, V. C.: Treatment of 134 Cases of Meningococcic Infection with Massive Doses of Sulfadiazine, Am. J. M. Sc. *207*:67-77, Jan. 1944.

Sulfadiazine in an initial oral dosage of 8 Gm. followed by 3 or 4 Gm. every four hours was administered to 134 patients with meningococcic infections. In some instances sulfanilamide was substituted

when renal toxicity due to sulfadiazine interfered with adequate chemotherapy. Although a high incidence of toxic reactions was observed (28 per cent), the mortality rate was only 3.1 per cent, and none of the deaths could be attributed to the drug. It was concluded, therefore, that massive doses of sulfadiazine are justified, in conjunction with careful observation and supervision, for the treatment of meningococcic infections in seriously ill or moribund patients.

Kaplan, G.: Massive-Dose Sulfadiazine Therapy in Meningococcus Meningitis, New York State J. Med. *43*:2210-2212, Nov. 15, 1943.

In order to obtain as soon as possible blood levels of 20 mg. per 100 cc., ten meningococcic meningitis patients received 6 Gm. of sodium sulfadiazine intravenously and two were given 10 Gm. intravenously, followed by additional oral or intravenous doses. In most instances the patient was asymptomatic and afebrile within twenty-four or forty-eight hours. There were no deaths, and no drug reactions were observed except for transitory hematuria in two patients.

McDonald, J. B., and Johns, C. T.: Sodium Sulfadiazine in the Treatment of Meningococcal Meningitis, California & West. Med. *59*:268-271, Nov. 1943.

Although 6 of 10 patients with meningococcic meningitis were in coma for an average of twenty-seven hours, there were no deaths. Fulminant cases require an initial dose of 5 Gm. of sodium sulfadiazine intravenously followed by 1 Gm. every four hours intravenously in the presence of coma or vomiting, otherwise 1 Gm. of sulfadiazine orally for at least ten days. An average total dosage of 64 Gm. was employed, and blood levels of 5 to 12 mg. per 100 cc. were obtained. To prevent renal and toxic complications, fluids and sodium bicarbonate were given, and blood counts and urinalysis were performed frequently.

Other Infections

Tudor, R. B.: The Chemotherapy of Infantile Diarrhea: A Comparison of Sulfadiazine and Sulfapyrazine, J. Pediat. *22*:652-654, June 1943.

Fifteen infants ill with bacillary dysentery or parenteral diarrhea were treated with sulfadiazine and 22 with sulfapyrazine in a daily dosage of 0.1 Gm. per kilogram of body weight. Flexner Y organisms were found in the stools of three patients and Flexner V in a

fourth. These two sulfonamides were equally effective as therapeutic agents in both conditions. Toxic reactions were not encountered except for microscopic hematuria in three infants receiving sulfadiazine.

Winters, K. J., and Janney, F. R.: Sulfadiazine. Review of Its Use in Treatment of Children, Am. J. Dis. Child. *65*:702-711, May 1943.

Sulfadiazine was administered to 90 children for the treatment of a variety of conditions such as osteomyelitis, pneumonia, bronchitis, pharyngitis, tonsillitis, acute otitis media, empyema, cervical and axillary adenitis, meningitis, cellulitis, pyelitis and impetigo. This sulfonamide was found to be especially effective against hemolytic streptococci, pneumococci, Staphylococcus aureus haemolyticus, meningococci and Haemophilus influenzae. For the treatment of most infections a daily dosage of ¾ to 1 grain per pound of body weight is recommended, which will produce average blood levels of 7 to 10 mg. per 100 cc.

Satterthwaite, R. W.: Sulfadiazine Reactions; Their Frequency and Treatment in Urological Cases, J. Urol. *49*:302-315, Feb. 1943.

Sulfadiazine proved to be an effective chemotherapeutic agent for the treatment of urinary tract infections, especially those due to Proteus vulgaris, Pseudomonas aeruginosa and the gonococcus. Escherichia and Aerobacter infections responded as well to sulfadiazine as to sulfathiazole. Prophylactic use of this drug after operative procedures on urological patients has resulted in a decrease to 1 per cent in the incidence of upper respiratory tract complications. Fifty-eight toxic reactions occurred in 500 patients (11.6 per cent). These may be prevented by control of dosage and duration of therapy and by close observation of blood levels and blood counts.

Prophylactic Uses

Coburn, A. F.: Mass Sulfadiazine Prophylaxis of Respiratory Diseases in the U. S. Navy, Bull. New York Acad. Med. *21*:281-301, June 1945.

The prophylactic use of sulfadiazine in a dosage of 0.5 or 1.0 Gm. daily was evaluated in approximately 600,000 Naval personnel in comparison with a control group of 300,000.

A decrease in the incidence of streptococcic respiratory infections was observed at the end of the first week of treatment, and by the

end of one month the incidence of scarlet fever, tonsillitis and rheumatic fever declined to a low level. Hospital admissions for respiratory diseases numbering from 5 to 18 per 1,000 per month decreased to less than 1 per 1,000 per month. Meningococcic infections were eliminated, and at some Naval stations, pneumonia cases were reduced by 50 to 80 per cent.

Hodges, R. G.: The Use of Sulfadiazine as a Prophylactic Against Respiratory Disease, New England J. Med. *231*:817-820, Dec. 21, 1944.

A sharp increase was noted in hospital admissions due to streptococcic and pneumococcic infections in a large military group. For prophylactic purposes sulfadiazine was given in a daily dosage of 1 or 2 Gm.

This drug had the greatest effect on the incidence of streptococcic infections, reducing to almost zero the number of cases of follicular tonsillitis and scarlet fever. Pneumococcic infections also were prevented. Since pneumococcic were typed from 75 per cent of the patients with lobar pneumonia, the reductions in incidence was believed to be due to the effect of sulfadiazine on the pneumococci. Evidence of the prophylactic effectiveness of sulfadiazine against ordinary respiratory disease and acute rheumatic fever also was obtained.

Lewis, W. B., Bolker, H., and Klein, D.: Mass Treatment with Sulfadiazine —Its Effect During an Outbreak of Meningococcus Meningitis, Mil. Surgeon *93*:443-447, Dec. 1943.

During an outbreak of meningococcic meningitis in an Army camp, the carrier rates in military and civilian groups were found to be 12.5 per cent and up to 42.3 per cent respectively. All carriers were admitted to hospital and received 2 Gm. of sulfadiazine daily for two days, followed by 1 Gm. daily for two days, and in some instances sulfanilamide in addition. All but one became negative after sulfadiazine or subsequent sulfanilamide therapy. Elimination of the carriers appeared to control the disease.

Subsequent prophylactic administration of sulfadiazine was instituted in the entire military and civilian camp personnel while on duty. No new case of meningitis occurred except for one in an untreated control group, and the carrier rate one month after sulfadiazine therapy was found to be 0.75 per cent.

Watson, R. F., Schwentker, F. F., Fetherston, J. E., and Rothbard, S.: Sulfadiazine Prophylaxis in an Epidemic of Scarlet Fever, J. A. M. A. *122*:730-733, July 10, 1943.

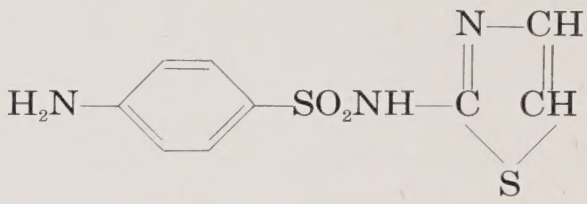
During an epidemic of scarlet fever at a Naval station, due to the group A, type 19 hemolytic streptococcus, the number of cases increased to approximately 10 a week. One group was started on 1 Gm. of sulfadiazine daily for thirty-two days and this resulted in a sharp drop in hospital admissions for scarlet fever, while the incidence in the untreated controls remained high. Both groups then received sulfadiazine for twelve days, resulting in complete remission of the disease until the end of the observation period sixteen days after sulfadiazine was discontinued. Sick calls due to respiratory complaints also decreased.

Kuhns, D. M., Nelson, C. T., Feldman, H. A., and Kuhn, L. R.: The Prophylactic Value of Sulfadiazine in the Control of Meningococcic Meningitis, J. A. M. A. *123*:335-339, Oct. 9, 1943.

Sulfadiazine was given orally in a dosage of 3 Gm. daily for three days or 2 Gm. daily for two days to more than 15,000 soldiers at two Army posts. The incidence of meningococcic meningitis dropped sharply, only 2 cases occurring during the eight week observation period in contrast to 40 cases among 18,800 untreated controls. The carrier rate in the treated group was reduced from over 30 per cent to approximately 2 per cent and even to zero, while in the control group the rate remained high and on several occasions was found to have increased.

Sulfathiazole

Formula: Sulfathiazole—2-(p-aminobenzenesulfonamido)-thiazole—is another heterocyclic derivative of sulfanilamide. It is represented by the structural formula

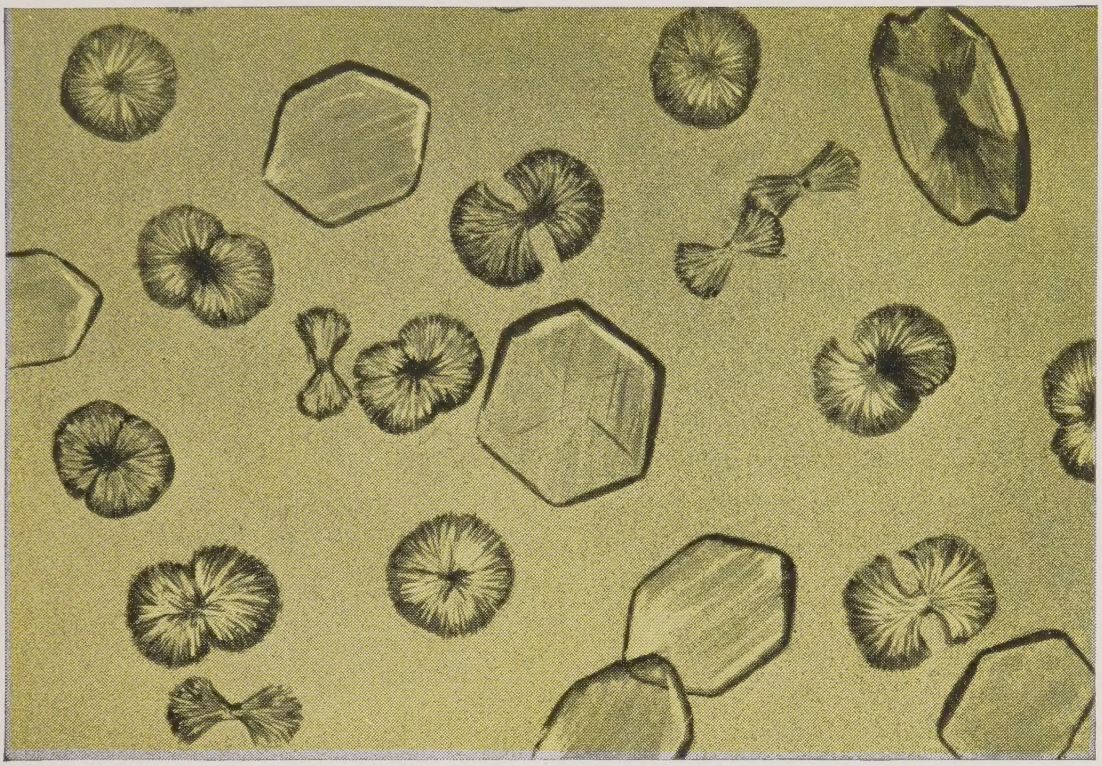


Sulfathiazole is a white, crystalline powder, poorly soluble in water and insoluble in benzene, chloroform, ether, ethyl acetate and ethylene dichloride. It is soluble in dilute mineral acid solutions, alkali metal hydroxide and carbonate solutions.

Characteristics: Sulfathiazole is characterized by rapid absorption and quick action. It is more rapidly absorbed from the gastrointestinal tract than sulfadiazine, and more rapidly eliminated by the kidneys. Because of its more rapid excretion, the compound does not maintain therapeutic blood levels as long as sulfadiazine. Sulfathiazole diffuses into the body fluids fairly quickly, except into cerebrospinal fluid, where diffusion is delayed and the final concentration is low.

Sulfathiazole is less toxic than sulfanilamide but slightly more toxic than sulfadiazine.

Indications: Sulfathiazole may be administered in *pneumococcic infections* such as pneumonia, otitis media and peritonitis; *gonorrhea; gonococcic infections* such as arthritis and ophthalmia; *staphylococcic infections* such as sepsis, pneumonia, carbuncles and



Sulfathiazole may appear also as acetylsulfathiazole in urine. The crystals have the appearance of shocks of wheat with a central binding. These may present all degrees of fullness up to a stage where they form two half circles fused at the center. They may also form complete rosettes. Another form is that of hexagonal platelets of variable density which may be indented at ends and show an envelope-like marking.

osteomyelitis; *Escherichia coli infections* such as tissue infections and urinary tract infections; and *infections* due to *Pseudomonas aernginosa.*

Possible *prophylactic* uses of the compound include burns, peritonitis, urinary tract infections and otitis media.

Dosage: Initial oral dose for adults is 4 Gm. This is followed by a maintenance dose of 1 Gm. every four hours until the patient's temperature has been normal for 72 hours. See page 47 for detailed dosage schedule.

How Supplied: Sulfathiazole U. S. P. is supplied in 0.5-Gm. tablets in bottles of 100, 500 and 1,000.

Sulfanilamide

Formula: Sulfanilamide (p-aminobenzenesulfonamide) is the parent drug of the sulfonamides. The amide of sulfanilic acid, it is represented by the structural formula

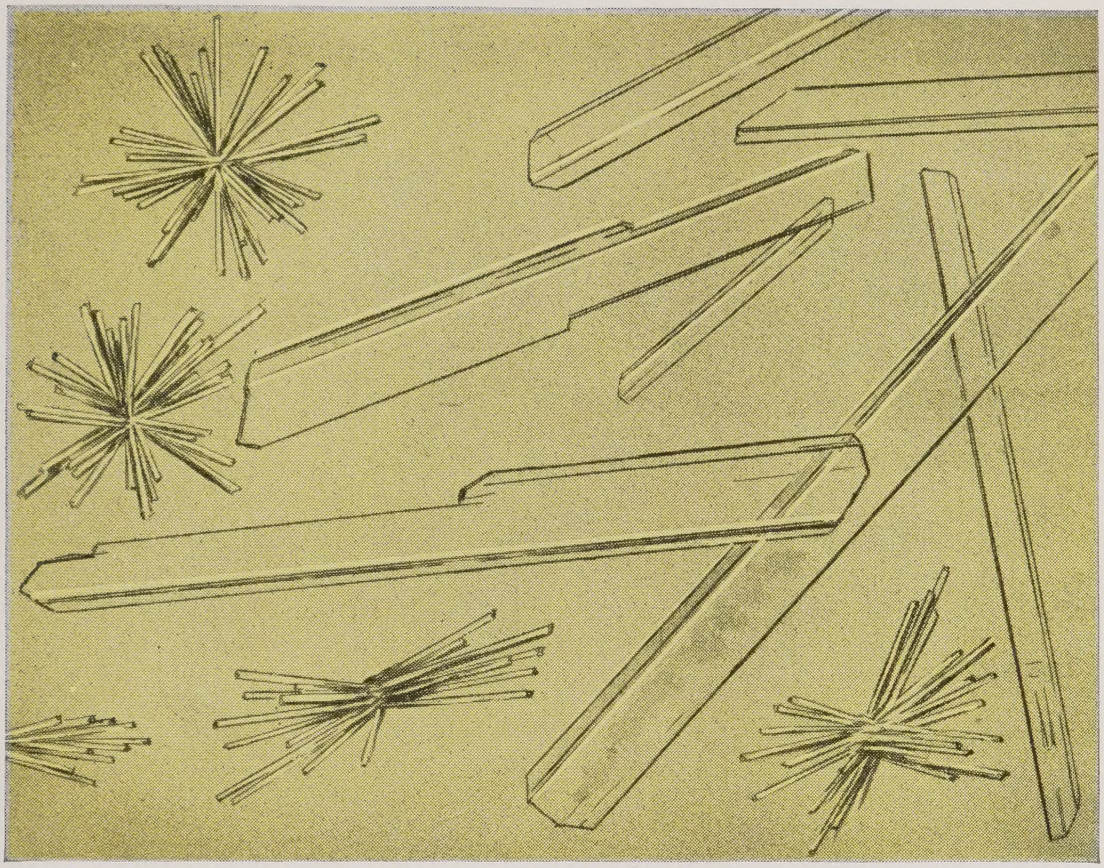
Sulfanilamide is a white, practically odorless crystalline substance, soluble in hot water, hot alcohol and cold acetone. It is slightly soluble in cold water and cold alcohol, and insoluble in ether, benzene and chloroform.

Characteristics: Sulfanilamide is characterized by ready absorption and quick diffusion into body tissues and fluids. While it is not as rapidly absorbed from the gastrointestinal tract as sulfathiazole, it is more slowly eliminated by the kidneys. However, sulfanilamide is characterized by more rapid renal excretion than sulfadiazine.

The toxicity of sulfanilamide is regarded as moderate. The compound is more toxic than sulfathiazole.

Indications: Sulfanilamide may be administered for treatment of *beta hemolytic streptococcic infections* such as meningitis, septicemia, puerperal sepsis and Ludwig's angina; *meningococcic meningitis, chancroid, gas gangrene, proteus infections, brucellosis, trachoma, lymphogranuloma venereum* and *actinomycosis.*

Possible *prophylactic* uses include burns, compound fractures, susceptible scarlet fever contacts, extensive tissue wounds, gunshot wounds, otitis media, peritonitis and rheumatic fever.



Sulfanilamide and acetylsulfanilamide crystals may be found in the urine but are not common except when the blood concentration is very high. Sulfanilamide appears as long transparent crystals with a tendency to aggregate. Acetylsulfanilamide forms sheaves and radiating bundles of prismatic crystals.

Dosage: Sulfanilamide dosage depends upon the severity of the infection. Severe infections require a blood concentration of approximately 10 mg. of the drug per 100 cc., while in mild to moderately severe infections a concentration of from 5 to 10 mg. per 100 cc. may be sufficient. See page 47 for detailed dosage schedule.

How Supplied: Sulfanilamide U. S. P. is supplied in 0.3-Gm. tablets in bottles of 100, 500 and 1,000, and in 0.5-Gm. tablets in bottles of 100 and 500.

SULFONAMIDE DOSAGE CHART

SULFONAMIDE	DISEASE	DOSAGE			
		ADULTS		CHILDREN	
		INITIAL DOSE	DAILY MAINTENANCE DOSE	INITIAL DOSE	DAILY MAINTENANCE DOSE
'SULFATHALIDINE' Phthalylsulfathiazole 2-(N⁴-phthalyl-sulfanilamido)-thiazole	Ulcerative colitis Regional ileitis and ileo-jejunitis	0.1 Gm. per Kg. of body weight	0.1 Gm. per Kg. of body weight in 4 or 6 divided doses. Reported effective also when given in dose of 3 Gm. daily.	Same as for adults.	
	Preoperative preparation	0.125 Gm. per Kg. of body weight beginning 2 to 4 days before operation.	0.125 Gm. per Kg. of body weight divided into 6 parts and given every 4 hours.	Same as for adults.	
	Postoperative treatment	Continue same dosage as before operation beginning as soon as patient can take an ounce of warm water without undue nausea.		Same as for adults.	
'SULFASUXIDINE' Succinylsulfathiazole 2-(N⁴-succinyl-sulfanilamido)-thiazole	Preoperative preparation	0.25 Gm. per Kg. of body weight beginning 3 to 5 days before operation.	0.25 Gm. per Kg. of body weight divided into 6 parts given every 4 hours.	Same as for adults.	
	Postoperative treatment	Continue same maintenance dose as before operation, beginning as soon as patient can take an ounce of warm water without undue nausea.		Same as for adults.	
	Bacillary dysentery Ulcerative colitis Regional ileitis and ileo jejunitis	0.25 Gm. per Kg. of body weight	0.25 Gm. per Kg. of body weight divided into 6 parts and given every 4 hours.	Same as for adults.	
	E. coli infections of genito-urinary tract	0.25 Gm. per Kg. of body weight in 4 or 6 divided doses for 1 week.	0.125 Gm. per Kg. of body weight for from 1 to 2 weeks.	Same as for adults.	
SULFAMERAZINE (4-methyl-2-sulfanilamido-pyrimidine)	Pneumococcic pneumonia Hemolytic streptococcic infections Meningococcic meningitis	3 to 6 Gm. depending on severity of illness.	1 Gm. every 8 hours.	Under 6 months: 0.5 Gm. 6 months to 3 years: 1 Gm. 3 to 10 years: 1.5 Gm.	Under 6 months: 0.25 Gm. every 12 hours. 6 months to 3 years: 0.5 Gm. every 12 hours. 3 to 10 years: 1 Gm. every 12 hours.
	Gonorrhea	1.5 Gm.	1.5 Gm. every 12 hours.	Dosage in proportion to age and weight of child.	
	COMBINED THERAPY WITH SULFAMERAZINE AND SODIUM SULFAMERAZINE				
	Pneumococcic pneumonia with septicemia Severe hemolytic streptococcic infections Severe meningococcic meningitis	0.05 Gm. of sodium sulfamerazine per Kg. of body weight administered intravenously and made up in appropriate dilution in sterile distilled water.	1 Gm. orally every 8 hours.	0.05 Gm. of sodium sulfamerazine per Kg. of body weight administered intravenously and made up in appropriate dilution in sterile distilled water.	Under 6 months: 0.25 Gm. orally every 12 hours. 6 months to 3 years: 0.5 Gm. every 12 hours. 3 to 10 years: 1 Gm. every 12 hours.
			To obtain the approximate intravenous dose of sodium sulfamerazine in grams divide the body weight in pounds by 40.		

SULFADIAZINE 2-(p-aminobenzene-sulfonamido)-pyrimidine	Pneumococcic pneumonia	0.1 Gm. per Kg. of body weight.	1 Gm. every 4 hours day and night until temperature has been normal for 3 days.	0.1 Gm. per Kg. of body weight.	Total daily dose of 0.1 Gm. per Kg. of body weight divided into 6 parts given at 4 hour intervals day and night until temperature has been normal for 48 hours.
	Mild or moderately severe hemolytic streptococcic infections	0.05 Gm. per Kg. of body weight.	0.1 Gm. per Kg. of body weight divided into 6 parts given every 4 hours day and night until temperature has been normal for 5 days.	Same as for adults.	
	Gonorrhea	3.0 Gm.	1 Gm. every 6 hours for 5 days. If blood count remains normal continue therapy for a total of not more than 8 days.	Dosage in proportion to age and weight of child.	
	COMBINED THERAPY WITH SULFADIAZINE AND SODIUM SULFADIAZINE				
	Pneumococcic pneumonia	0.06 Gm. of sodium sulfadiazine per Kg. of body weight made up as 5% solution in sterile distilled water administered intravenously.	1 Gm. of sulfadiazine by mouth every 4 hours day and night until temperature has been normal for 3 days.	Same as for adults.	
	Severe hemolytic streptococcic infection	0.06 Gm. of sodium sulfadiazine per Kg. of body weight made up as 5% solution in sterile distilled water administered intravenously.	0.1 Gm. of sulfadiazine per Kg. of body weight divided into 6 doses given by mouth at 4 hour intervals day and night until temperature has been normal for 5 days. Then decrease dose slowly until patient is ambulatory.	Same as for adults.	
SULFATHIAZOLE 2-(p-aminobenzene-sulfonamido)-thiazole	Pneumococcic pneumonia	4.0 Gm.	1 Gm. every 4 hours day and night until temperature has been normal 72 hours.	0.15 Gm. per Kg. up to 25 Kg. of body weight.	0.15 Gm. per Kg. up to 25 Kg. of body weight divided into 4 parts given every 6 hours day and night until temperature has been normal for 48 hours.
	Gonorrhea	0.5 Gm. every 3 hours for 6 doses on the first day of treatment.	2.0 Gm. per day for not more than 10 days. If no improvement by 5th day shift to sulfapyridine. Do not continue drug therapy more than 15 days.	Dosage in proportion to age and weight of child.	
	Staphylococcic pneumonia	4.0 Gm.	1 Gm. every 4 hours day and night until temperature has been normal for 5 days. If satisfactory results are not obtained increase daily dose by 25% to 50%.	0.15 Gm. per Kg. up to 25 Kg. of body weight.	0.15 Gm. per Kg. up to 25 Kg. of body weight divided into 4 parts given every 6 hours day and night until temperature has been normal for 5 days. If satisfactory results are not obtained increase daily dose by 25% to 50%.
	Staphylococcic cellulitis and lymphangitis	4.0 Gm.	1.5 Gm. every 4 hours day and night until infection is controlled. Then 1 Gm. every 4 hours day and night for 7 days.	Dosage in proportion to age and weight of child.	
	Staphylococcic bacteriemia	4.0 Gm.	1.5 Gm. every 4 hours until temperature has been normal for 48 hours; then 1.0 Gm. every 4 hours for 14 days; then 0.5 Gm. every 4 hours for an additional 2 weeks.	Dosage in proportion to age and weight of child.	
SULFANILAMIDE (p-aminobenzene-sulfonamide)	Severe infections	0.10 Gm. per Kg. of body weight.	Total daily dose of 0.10 Gm. per Kg. of body weight divided into 6 parts given every 4 hours day and night until temperature has been normal for 7 days.	Same as for adults.	
	Mild and moderately severe infections	Total daily dose of 0.10 Gm. per Kg. of body weight divided into 6 parts and given every 4 hours day and night until temperature has been normal for 5 days.		Same as for adults.	

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